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Measles outbreaks in Italy: A paradigm of the re-emergence of vaccine-preventable diseases in developed countries

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Measles outbreaks in Italy: a paradigm of the re-emergence of vaccine-preventable diseases in developed countries.

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Background

The last decade has seen a worrying re-emergence of outbreaks of vaccine-preventable diseases (VPDs) across developed countries* worldwide. According to the European Centre for Disease Prevention and Control (ECDC), 14732 cases of measles were reported in the European Union between February 2017 and January 2018, with Romania and Italy accounting for the vast majority of the cases (35% and 34%, respectively)(1). Suboptimal vaccination coverage was identified as the key causative factor, with 87% of the affected individuals being unvaccinated. Similarly, a recent epidemiologic assessment of the 2013 measles outbreak in New York City indicated that 78% of the infected individuals were "unvaccinated owing to parental refusal or intentional delay"(2). The direct cost of the outbreak to the New York City Department of Health and Mental Hygiene was estimated as $394,448 and a total of 10,054 working hours. Measles outbreaks have recently also been reported in other developed countries including Japan(3), Australia(4), and New Zealand(5).

It is worth emphasising that while measles vaccine coverage is around or above 90% in all of the countries mentioned, the critical coverage threshold to provide effective herd immunity against measles is estimated to be in the 91%-94% range, with recent studies suggesting a higher (>95%) threshold value(6-8). Moreover, even in countries where the average vaccine coverage of the population is above the herd immunity threshold, it is not uncommon for small localised communities to have significantly lower coverage, thereby acting as "hot spots" for the onset of outbreaks(9). It has been proposed that "measles is often the first vaccine preventable disease detected following a breakdown in routine immunization activities, and as such is a 'canary in the coal mine', and a leading indicator of the status of vaccination programs"(8). A clear example of this phenomenon is the sudden increase in measles incidence observed in the aftermath of the 2014 West Africa Ebola outbreak and in war-affected Middle-Eastern countries(10-12).

This paper seeks to evaluate the social, cultural, political and epidemiological factors underpinning the recent measles outbreaks in Italy; this perspective, after considering the context-specific contingencies, could offer a novel viewpoint to the ongoing discourse on the re-emergence of measles or other vaccine-preventable diseases in other developed countries.

*In the present paper, the expression "developed countries" is used to indicate countries that are defined as having "developed economies" according to the groupings delineated by the United Nations in the statistical annex of the latest World Economic Situation and Prospect report(13).

Outline of measles pathology and epidemiology

Measles is a highly contagious exanthematic disease caused by single-stranded RNA viruses of the genus *Morbillivirus*, part of the *Paramyxoviridae* family(14). The Measles Virus (MeV) is transmitted from infected individuals via physical contact and aerosol, with infection occurring via the respiratory route. Traditionally, the initial event of measles infection has been considered to be the adhesion of MeV to epithelial cells in the host's respiratory tract. However, as infection requires the hemagglutinin-mediated binding of the virus to CD150, which is not expressed on the apical surface of respiratory epithelial cells, it has been proposed that $CD11c^+$ myeloid cells (alveolar macrophages and dendritic cells) might represent early target cells instead(15). MeV is then thought to spread to the bronchus-associated lymphoid tissue (BALT), which is rich in $CD150^+$ lymphocytes and constitutes

a site of efficient MeV replication(16). After infection of lymphoid tissue (BALT and lymph nodes) the virus migrates to other tissues and organs through systemic dissemination of circulating infected $CD150^{+}$ lymphocytes.

Early clinical symptoms of measles typically manifest themselves 9-19 days after infection with the onset of elevated temperature associated with cough, coryza and conjunctivitis, colloquially known as "the three Cs"(14). The characteristic maculopapular skin rash develops around 2-4 days after the early symptoms, with small red-brown spots initially appearing around the head, neck and face, and progressively spreading to the trunk and limbs. In most cases the illness is resolved within less than two weeks from the onset of the symptoms, with the host's immune system attacking and eliminating MeV-infected cells. However, it is well-known that measles infection can result in serious complications especially in categories at risk such as babies, children with a poor diet, immuno-compromised individuals, and pregnant women(17). Commonly reported complications include diarrhoea, pneumonia, ear and eye infections, and a risk of miscarriage/stillbirth in pregnant women. Complications arising from measles have a multifactorial aetiology and can result in lifelong disabilities and death. The case fatality ratio (CFR) of measles has been estimated to range in average from less than 0.01% in developed countries to over 5% in developing countries, reaching figures as high as 40% in some communities(18, 19). Measles is considered as one of the most infective viruses, with a basic reproduction number ($R_{0,}$ a metric typically used to determine the potential of an infection to spread within a population) estimated in the range of 9-18, greatly exceeding, to name a few, that of poliomyelitis (4-13), smallpox (5-7), Spanish influenza (1.5-3.8), Ebola (~4.5), and Zika (~2)(8, 20).

According to the World Health Organization (WHO), "The disease remains one of the leading causes of death among young children globally, despite the availability of a safe and effective vaccine"(21). In 2012, the WHO launched the Global Measles and Rubella Strategic Plan 2012-2020 with the aim to "protect and improve the lives of children and their mothers throughout the world, rapidly and sustainably"(22). The WHO's strategy is based on five key action points, the first of which is to "achieve and maintain high levels of population immunity by providing high vaccination coverage with two doses of measles- and rubella-containing vaccines". A midterm review of the WHO strategic plan highlighted how "significant gains toward measles elimination have been made in the past 15 years with an estimated 79% reduction in global measles mortality between 2000 and 2014 resulting in over 17 million measles-related deaths averted"(23). According to the authors of the midterm review, these results could largely be attributed to the 11% increase in WHO member states providing a second dose of measles-containing vaccine (MCV2), raising MCV2 coverage from 48 to 56%.

The prophylactic effectiveness of measles vaccines has been attributed to the virus' antigenic stability(24). Despite the genotypic diversity of MeV strains, the virus can be considered serologically monotypic, meaning that polyclonal antibodies raised against one strain (e.g. the strain used in the vaccine) can recognise and neutralise all other viral strains(8). As highlighted in a recent WHO position paper, "The available live attenuated measles vaccines are safe and effective, provide long-lasting protection, are inexpensive and may be used interchangeably within immunization programmes"(25). Although no pharmaceutical formulation is exempt from side effects, the proven benefits of measles vaccination have been time and again demonstrated to largely out measure the rare contraindications associated with it (26, 27).

Over the last decades, significant concerns have been raised regarding alleged links between vaccination and the development of autism spectrum disorder, an effect often ascribed to the use of the mercury-containing antiseptic thiomersal as a preservative in vaccine formulations. As will be

discussed in more details in the next chapter, despite overwhelming evidence supporting the absence of a link between vaccines and autism these concerns and rumours still have a significant impact on the vaccination decision-making process amongst the general population(28, 29).

Parental hesitancy and refusal

In the last two decades, the affirmation of movements (often referred to as "anti-vax") openly opposing the practice of vaccination has typically been associated with the controversy spurred by Andrew Wakefield's infamous 1998 Lancet paper, which suggested a causative link between the measles, mumps and rubella (MMR) vaccine and the onset of intestinal abnormalities and behavioural disorders, most notably autism(30). It is widely acknowledged that the global availability of internet access played a significant part in the development and affirmation of anti-vax movements. Notwithstanding its undeniable importance in global communication and knowledge exchange, the World Wide Web has been defined, due to its decentralised and largely uncontrolled nature, as "a postmodern Pandora's box" through which misleading (and in many cases downright mendacious) information can reach a huge audience worldwide in an extremely short time(31) . The retraction of Wakefield's paper in 2010 and the decision of the British General Medical Council to withdraw his medical licence did not reduce the spread of misinformation on the matter nor the consolidation of anti-vaccination feelings amongst the general population(32). When striving to understand the nature and causes of the diffusion of anti-vax movements, it is essential to stress how the phenomenon predates Wakefield's work by several decades. Soon after the first law on compulsory vaccination (the 1853 Vaccination Act) was promulgated in England, opposition movements contesting the practice arose in virtually all countries where legislation on the matter existed(32). Since their inception, movements opposing state-mandatory vaccination have been widely diverse in terms of the reasons underpinning their stance and its extent, ranging from scepticism to civil disobedience and violent protest. When evaluating the causes underpinning vaccine hesitancy and refusal, it is important to consider the wider social context in which the decision-making process takes place(33). Through history, opposition to vaccination has been motivated by a combination of different factors including religious or moral convictions, scepticism on the effectiveness of vaccines, peer advice/pressure, distrust of authority, alternative/holistic approaches to healthcare, conspiracy theories, *et cetera* (31-36). Another key contributory cause of vaccine hesitancy is complacency, whereby the necessity of immunisation against VPDs ,the impact of which has been greatly reduced through the practice of vaccination, is underestimated amongst the population(37). In that sense, it is often said that vaccines are victims of their own success: complacency resulting from near-elimination of many VPDs has a negative impact on the vaccination decision-making process, with parents often deeming vaccination against nearly-eradicated diseases not to offer benefits worth the perceived risks and stress associated with vaccinating their children.

As will be discussed in more detail in the next section, measles vaccine coverage in Italy, which had increased steadily since its introduction in the 1970s, decreased significantly between 2010 and 2015. A study published in 2017 investigated "the web and public confidence in MMR vaccination in Italy"(38). The study unearthed a significant inverse correlation between the volume of Google searches, Tweets, and Facebook posts containing specific keywords (the Italian words for "vaccines", "autism", "MMR", "measles", etc.) and the MMR vaccination coverage over the same time period (2010-2015). Although it would be inherently difficult to establish a causative link between the two variables, it is reasonable to speculate that internet activity can be a powerful indicator of the population's attitude towards vaccination.

Recently, a survey was carried out by Italian news outlet “La Stampa” to investigate the opinions and disposition of the Italian public on the matter of compulsory immunisation(39). This survey found that 28% of the participants were against compulsory vaccination of school-age children, while 69% expressed a favourable opinion. Strikingly, the two main reasons underpinning opposition to compulsory immunisation were of social/political nature: 10% of the participants oppose compulsory vaccination “because it [compulsory vaccination] is in the interest of pharmaceutical companies”, and 7% “because it is against freedom of thought/choice”. A smaller share of respondents adduced more strictly medical/scientific concerns, such as “because of the absence of pre-vaccination screening” (3%), “because they [the vaccines] are too strong for children” (2%), and “because they are harmful as they could contain heavy metals and lead to autism” (2%). An inverse trend could be observed amongst participants who declared to be in favour of compulsory vaccination, who mostly adduced medical/scientific justifications to their choice: “because vaccines save lives” (26%), “because they eliminated last century’s diseases” (18%), “because they prevent serious diseases” (15%), and “because there are no studies stating that they are harmful” (4%). Only 2% of participants declared to support compulsory vaccination “because state laws have to be respected”.

History of measles incidence and mortality in Italy

The systematic collection and categorisation of statistical data on the Italian population can be dated back to 1926 with the establishment of the Central Institute for Statistics which is now known, after changing name in 1989, as the Italian National Institute of Statistics (ISTAT).

In 1931, the Central Institute for Statistics released an extensive report on the causes of death of the Italian population from 1887 to 1929(40). According to the report, measles mortality dropped from 80.3 to 10.0 deaths per 100,000 inhabitants in the analysed period. The decline was not steady, but rather followed an oscillatory pattern, with the most significant peak observable in 1916, presumably as a consequence of Italy’s involvement in World War I in 1915. Significant regional differences were also highlighted in the report, with measles mortality in 1927 ranging from 0.4 to 49.6 deaths per 100,000 inhabitants in the Marche and Calabria regions, respectively. Measles mortality continued to drop in the years leading to World War II, with 8.3 and 4.6 fatalities recorded per 100,000 inhabitants in 1931 and 1936, respectively (41). A more recent Central Institute for Statistics report, published in 1953, highlighted a comparable trend: measles mortality continued to decline in an oscillatory fashion from 4.8 to 1.2 deaths per 100,000 inhabitants in the 1937-1950 period(42). The 1953 report confirmed the observation of a wide variability between different regions, with no measles-ascribable fatalities in 1950 in three northern regions (Valle d'Aosta, Trentino-Alto Adige, Friuli-Venezia Giulia), and a mortality of 7.4 deaths per 100.000 inhabitants in the southern region of Basilicata in the same year.

Measles mortality continued to decline in the following years, reaching less than 1 death per 100,000 inhabitants in the early 1950s, with significantly higher figures observed amongst young children(43). Albeit in a mostly anecdotal fashion, the 1931 Central Institute of Statistics report had already highlighted how measles is considerably more lethal in children than in adults; a more recent ISTAT report estimated that the overall mortality of Italian children younger than 1 year was around 34.7% of live births in 1887, with measles reportedly accounting for 3% of deaths(44). Child mortality figures have declined steadily over the years (again with the noticeable exception of a sharp peak in correspondence with World War I), with the rate of children dead within a year of birth reaching 0.4% of total live births in 2011.

The earliest available data for the incidence of measles amongst the Italian population refer to the 1881-1890 period, when an average of 162,076 cases were reported every year, equivalent to 540.3 cases per 100,000 inhabitants(45). The number of measles cases declined following an oscillatory trend over the following decades, reaching an average of 70,635 cases (137 per 100,000 inhabitants) in the 1961-1965 period. A clear inverse correlation between measles incidence and vaccine coverage could be observed in the years followings the introduction of a single-antigen measles vaccine in 1976 (46, 47). The MMR vaccine was phased in to Italy in its current formulation in the early 1990s, followed in 1999 by the recommendation that a second vaccine dose be administered in regions with over 80% coverage for the first dose(46). In 2003, in an attempt to eradicate endemic measles and rubella transmission by 2007, the Italian Ministry of Health launched the National Plan of Measles and Congenital Rubella Elimination (PNEMoRC), recommending the introduction of two MMR doses in all Italian regions towards the target of achieving 95% vaccine coverage(48). In the following years, MMR vaccine coverage continued to increase amongst the Italian population, with single-dose coverage reaching a maximum of 90.6% in 2010. Worryingly, MMR coverage started to decline steadily after 2010, reaching a minimum of 85.2% in 2015(47). The downward trend appeared to be reversing since then, with coverage increasing to 87.3% in 2016 and 90.6% in 2017(49). The years following the dip in MMR vaccine coverage saw the re-emergence of measles outbreaks in Italy: 844 cases of measles were reported in 2016 compared to 251 in 2015, with incidence increasing from 0.4 to 1.4 cases per 100,000 inhabitants(50). In 2017, 4991 measles cases (4 of which fatal) were reported, with incidence soaring to 8.2 cases per 100,000 inhabitants(51). Data from the first six months of 2018 indicate that the outbreak is not yet resolved, with 2029 measles cases and 4 more fatalities reported from January to June 2018, with a provisional incidence of 6.7 measles cases per 100,000 inhabitants(52). As in the cases that were described earlier on in this chapter, significant regional differences can be observed in the ongoing measles outbreak in Italy. In 2017, 90% of the total measles cases were reported in just 8 of the 20 Italian regions, with incidence ranging from 0.6 cases per 100,000 inhabitants in Molise and Puglia to 28.8 cases per 100,000 inhabitants in Lazio(51). Similar observations were reported in the first six months of 2018, with 7 regions accounting for nearly 90% of all measles cases in Italy, and incidence ranging from no cases so far in Molise to 42.2 cases per 100,000 inhabitants as reported in Sicily(52).

The issue of vaccination in the current Italian political discourse

Over the last decade, the topic of compulsory vaccination has frequently hit the media spotlight and is currently the object of heated debate in the Italian social and political panorama. In July 2017, following the onset of the measles outbreak , the Italian government introduced a law (n.119, 31/7/2017) increasing the number of compulsory childhood vaccinations to ten (reduced from the twelve vaccinations proposed in the initial draft)(53). Moreover, it was ruled that non-compliance with the mandatory vaccination schedule would result in exclusion of unvaccinated children from nurseries and schools, with the exception of children who have already contracted the disease and those with a certified risk of adverse reactions to the vaccinations. The promulgation of the 2017 law rekindled the already heated controversy on mandatory vaccinations, and was met with widely discordant reactions amongst the Italian political class and general population alike. A vast proportion of the Italian public approved the new regulation, with public health representatives acknowledging that “government action was epidemiologically justified”(39, 54). However, several political exponents and a consistent part of the electorate criticised the new legislation, which was perceived as draconian and damaging to the citizens’ personal freedom(55, 56). The opposition to mandatory vaccination is particularly vocal amongst members and supporters of the “Five Star

Movement" (Movimento 5 Stelle, M5S), a populist party currently in a government coalition with the far-right League (formerly Northern League). Since its foundation in 2009, the Five Star Movement has gained increasing popularity amongst the Italian electorate, becoming the largest individual party in the 2018 general elections(57). The Five Star Movement presented itself as a novel web-based alternative to the corrupt Italian ruling class, gathering a wide array of anti-establishment feelings often bordering on markedly conspiratorial worldviews(58). Although M5S has recently taken an official position in support of mandatory immunisation, anti-vaccination feelings are frequently voiced by its exponents and supporters, with frequent references to pharmaceutical companies ("Big Pharma") allegedly lobbying to impose useless or even harmful vaccines upon the population(59, 60). Despite the Five Star Movement's official position on mandatory immunisation, the M5S Minister of Health Dr Giulia Grillo ruled that parents be allowed to self-certify that their children have received or will soon receive all the compulsory vaccinations, *de facto* meaning that parents will be allowed to enrol children into nursery or school without having to present a certificate of vaccination(61). In August 2018, members of parliament from the M5S-League coalition proposed amendments to the n.119 31/7/2017 law suspending for at least a year the requirement for parents to provide evidence or self-certification of compliance to the ten mandatory vaccinations when enrolling children to nursery and schools(62). These decisions raised justifiable concerns regarding the welfare of children with health conditions incompatible with the administration of vaccines, concerns that were not attenuated by Dr Grillo's proposal to place immunosuppressed pupils in "protected classes" to limit their exposure to unvaccinated (and therefore potentially contagious) children(63).

Conclusions and future perspectives

While the re-emergence of measles outbreaks in Italy is a multifaceted phenomenon underpinned by a variety of factors, there is increasing evidence indicating that "the main reason for this outbreak is an accumulation of a large pool of measles-susceptible population due to sustained low uptake of measles vaccine in Italy over the years"(64). The existing regional differences in access to healthcare and infrastructures, combined with feelings of scepticism and hostility towards the practice of vaccination, can result in the formation of pockets of at-risk population as local vaccine coverage drops significantly below the effective herd immunity threshold. Moreover, heterogeneity in infectious diseases notification patterns has also been identified as a factor potentially contributing to the development of measles hot spots, with significant under-reporting affecting the Southern regions of Italy, leading to potential underestimation of measles incidence among the population(65).

Despite the implementation of the 2003-2007 PNEMoRc strategic plan and its 2010-2015 follow-up, measles vaccine coverage in Italy is still below the 95% target, with local figures reportedly as low as 10% below this target in some regions (66) . While it is essential that the government continues to offer free access to vaccination and enforce adhesion to the mandatory vaccination schedule, it is conceivable that a "top down" approach is no longer sufficient by itself to reach and maintain adequate levels of immunisation amongst the population. The political and social events following the promulgation of the n.119 31/7/2017 law seem to prove the Latin adage "*inventa lege, inventa fraude*", that can loosely be translated as "every law has a loophole". In order to achieve appropriate vaccination coverage, it would be advisable that the enforcement of statutory immunisation is corroborated by a widespread campaign of health education of the population. A key step towards that endeavour is to clearly identify and understand the reasons underpinning vaccine hesitancy and

refusal in order to dispel misconceptions and prejudices on the matter. Hence, healthcare workers (HCW) should resist the temptation to engage in an ideological conflict that would result in further polarisation of the public opinion and the consolidation of hostile feelings against the vaccination practice(32). It is widely acknowledged that hesitation in the vaccination decision-making process cannot be treated as a monolithic phenomenon, and Italian healthcare policymakers have shown awareness of its complexities. The endeavour that HCW receive adequate training to identify and discuss the diversity of factors leading to vaccine hesitancy is reflected, among other initiatives, by the translation in the Italian language and distribution among HCW of the "Let's talk about hesitancy" ECDC practical guide for public health programme managers and communicators(67).

These factors are not always related to ideological or political convictions; in fact, it has been argued that "identifying anti-vaccination groups with other social movements may ultimately have the opposite effect to that intended"(36). As discussed, complacency has a significant impact on parents' vaccination decision-making process. It has been observed that complacency is heavily linked with parents' trust in the local health services(68), which might aggravate the gap in vaccination coverage between different Italian regions due to the existing differences in terms of sanitary infrastructure and healthcare investment(69).

With long-term strategic plans having only partially met their intended targets, and the applicability of mandatory vaccination legislature being undermined by political opposition and popular scepticism, there is compelling evidence pointing to the necessity of supporting legislative action with a radical increase in scientific literacy of the Italian population with regards to the topic of immunity and vaccination(70). Towards this endeavour, it is imperative that governments and policymakers collaborate with healthcare and educational institutions towards the development and implementation of a pervasive education campaign on the Italian territory, particularly focusing their efforts on regions affected by low vaccination coverage and high underreporting of infectious diseases. Short-term efforts should be made by HCW to provide citizens of child-rearing age with adequate support towards a well-informed decision-making process with regards to childhood vaccination. Ideally, these delicate issues should be delivered in a familiar, non-threatening environment such as maternity classes or post-partum home visits. Short-term efforts should be coupled with longer-term education campaigns to ensure that the topic of immunisation and vaccination is appropriately covered at all levels in school curricula; in that regard, it would be advisable to implement outreach activities aimed at supporting and training educators towards the development of pedagogical strategies to raise awareness amongst tomorrow's citizens on the importance of immunisation.

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Conflict of interest

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Highlights

- Measles outbreaks have been reported in several developed countries over the last decade.
- Insufficient vaccine coverage has been identified as a key causative factor in most outbreaks.
- Italy accounts for over 30% of measles cases reported since 2017 in the European Union.
- The issue of mandatory vaccination is heavily debated in recent Italian political discourse.
- Diffuse scepticism towards the vaccination practice reported amongst the Italian population.