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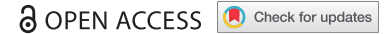


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REVIEW



## Countering vaccine hesitancy through immunization information systems, a narrative review

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### ABSTRACT

Immunization is one of the most important public health interventions to contrast infectious disease; however, many people nowadays refuse vaccination. Vaccine hesitancy (VH) is due to several factors that influence the complex decision-making process. Information technology tools might play an important role in vaccination programs. In particular, immunization information systems (IISs) have the potential to improve performance of vaccination programs and to increase vaccine uptake. This review aimed to present IIS functionalities in order to counter VH. In detail, we analyzed the automatic reminder/recall system, the interoperability of the system, the decision support system, the web page interface and the possibility to record adverse events following immunization. IIS could concretely represent a valid instrument to increase vaccine confidence, especially trust in both health-care workers and decision makers. There are not enough trials aimed to evaluate the efficacy of IIS to counter VH. Further researches might focalize on this aspect.

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### KEYWORDS

Immunization information system; vaccine; vaccine hesitancy; vaccines refuser; automatic reminder; vaccine confidence

## Introduction

### Vaccine hesitancy

Although vaccines represent one of the safest and most effective public health tools available to prevent and control infectious diseases, they are victims of their own success. Vaccine concern is as old as the vaccine itself, and although vaccines are safer than before, a recent review highlights discrepancy between scientific evidence and general perception.<sup>1</sup> There is no unique form of vaccine hesitancy (VH), nor a single reason behind this hesitancy: reasons are contextual (cultural, religious and geographical) and sometimes even vaccine specific.<sup>2</sup> According to the Strategic Advisory Group of Experts Working Group on Vaccine Hesitancy: “Vaccine hesitancy refers to delay in acceptance or refusal of vaccination despite availability of vaccination services”.<sup>3</sup> From the literature, it is known that vaccine hesitance is a continuum between full acceptors and total refusers.<sup>4</sup> Moreover, the 3 C model emphasizes complacency, convenience and confidence as factors that can influence the parents’ complex decision-making process on immunization. Complacency is determined by the reduction of perceived disease risk, due to the low incidence of the infection. Confidence is the trust in vaccine safety and effectiveness, and the trust in policy makers who decide for vaccinations. Convenience refers to the comfort, appeal and the quality of the service (real or perceived), including economic and geographic factors, but also the ability of people to understand priority placed on immunization.<sup>3,5,6</sup> As shown in the literature, the different proposed methods (i.e., reminder/recall and educational workshops) failed to motivate

the total refusers compared to late/selective refusers or cautious acceptors; nevertheless, communication approaches should take into account the various degrees of hesitancy.<sup>7</sup> The main public health issue related to VH is that the higher the VH, the less the vaccination rate, with decrease of herd immunity and higher risk of “old disease” outbreaks.<sup>8</sup> In other words, the increasing VH could jeopardize the individual and societal ability to prevent the impact of vaccine preventable diseases (VPD). To bridge VH, World Health Organization (WHO) proposes the use of a proactive and methodological communication strategy to face the misinformation and to contrast the anti-immunization movement. Tailored programs could reduce the unvaccinated pocket population, interrupt the infective transmission chain and reach the aims of eradication (polio) and elimination (measles and rubella).<sup>9</sup> Recently a review, published by Mayo Clinic experts, described what approach should be taken toward addressing VH.<sup>10</sup> They suggest (1) improving reminder/recall communications; (2) spreading vaccine schedules among physicians; (3) reducing as much as possible missed opportunities to delivery vaccines; (4) addressing hesitancy; (5) using a standard protocol; (6) having clear recommendations and (7) increasing pediatrician or general practitioner (GP) involvement in an immunization information system (IIS). Due to the cultural heterogeneity in VH, the proposed multiple approach should be tailored for each country, since it covers many of the key factors like offering an easy access to vaccination, communication mediated through health-care workers (HCWs), availability of information for action and understanding the reasons of VH.

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## IISs

IISs are confidential, electronic population-based systems storing individual-level data on vaccines received within a given geopolitical area.<sup>11</sup> These electronic registries store and provide access to consolidate personal immunization information. IIS has the potential to improve the performance of vaccination programs and to increase vaccine uptake. The importance of IIS and information technology tools for the vaccination programs was recognized by the Council of the European Union, in the Council Conclusions on 6 June 2011 on childhood immunization, followed by the Council Conclusions 1 December 2014 on vaccination: "...consider introducing or further developing immunisation information systems, including improved registration, where applicable, and pharmacovigilance systems".

Indeed IIS is also mentioned in the European Vaccine Action plan 2015–2020, the most recently launched global effort by the WHO.<sup>12</sup> Furthermore, European Centre for Disease Prevention and Control (ECDC) recently published a technical guidance aimed to provide support in plan, operation, management or continuous enhancement of IIS.<sup>13</sup>

IISs are also known as immunization registries, and in the majority of cases, data are entered by HCWs, whilst sometimes, the general population may also enter data, followed by a GP's approval. IISs are integrated systems in which all the entire process of vaccination is managed and recorded including the logistical aspect of the management of the vaccination services. So often, IIS is able to generate reminder and recall notifications, and it is largely used to assess vaccination coverage within a defined geographic area. Moreover, because in some countries, the vaccination services are private, the functions dedicated to recording of the vaccinated population are well separated from the other dedicated to the management of vaccination process and call of the people. Most IISs have additional capabilities, such as monitoring vaccine stocks to facilitate timely procurement of vaccines in order to limit wastage and ensure adequate supplies, as well as monitoring of adverse events following immunization (AEFI) reporting, and communicating with other health information systems, in particular with civil and cancer registries. The interoperability with civil registries allows the maintenance of birth-to-death vaccination histories, while the interconnection with the cancer registry is useful for efficacy/effectiveness study, particularly for vaccine-preventable cancers such as Hepatitis B virus (HBV) or HPV. Moreover, IIS can provide accurate data on which to make informed vaccination decisions and better protect against vaccine-preventable diseases. IISs have the potential to improve the performance of vaccination programs and to increase vaccine uptake; the strength of IIS is to provide decision makers with support for a vaccine strategy aimed to evaluate the efficacy of such vaccine policy and to improve program management. In our historical context, where VH is one of the most important challenges in the VPD field and since VH is a personal/community behavior choice in a specific context and for specific vaccines, it is important to know who, why and where VH is distributed (in socio-cultural, political, religious and geographical context). Even if the hesitants do not strictly match with not vaccinated, because it is possible that hesitants delay the vaccination; IIS could help to fight VH through recording additional information regarding

reasons for delay, interruption or refusal vaccinations. However, a review by Schuster et al. revealed gaps in knowledge especially due to the paucity of studies from middle- and low-income settings.<sup>1</sup> This is one of the possible applications of IIS for VH, also in the low- and middle-income countries, especially because several incoming countries are developing or piloting these instruments. The ECDC provided the last updating data on IIS implementation among European countries,<sup>14</sup> while WHO made available data for the other developing countries.<sup>15</sup>

## Study aim

The aim of this review was to present the advantages coming from the use of IIS as a tool able to counter VH. It is extremely important to take into account that VH is only one determinant of vaccine uptake and several other factors impact on that, such as vaccines supply, availability and accessibility to immunization services. In this paper, we only presented the IIS applicability on countering VH. In particular, we focalized our attention on: (1) automatic reminder/recall; (2) assessment of vaccines refusers and vaccines recipients characteristics; (3) interoperability with other electronic registries and decision support system; (4) evaluation of vaccine program performance; (5) possibility to record AEFI; (6) social mobilization to promote vaccine programs and (7) geographical distribution and clusters of vaccine hesitants. Each of the following aspects of IIS is discussed in reference to the 3C model, as depicted in Figure 1.

## Methods

We conducted a narrative review, as a comprehensive qualitative synthesis of previously published information.<sup>16</sup> The original research articles were retrieved from PubMed and Embase on June 2016, using a combination of MeSH term and free text words. The search terms were electronic, computerized, registr\*, register\*, immunization, immunisation, vaccin\*, "immunization registr\*", "immunisation registr\*", "vaccination registr\*", "vaccine hesitancy", barrier\*. Nevertheless, a manual check of the reference lists of the retrieved studies was carried out, in order to further identify proper articles. The articles were included in this narrative review whether they met the following inclusion criteria: (1) full text available; (2) articles using IISs as primary data source and (3) articles focusing on IIS's functionalities useful to counter VH (as previously detailed).

Exclusion criteria were: (1) studies without original data (abstract, letters to editor, editorials, comments and commentaries) and (2) studies published in Congress proceedings and gray literature. No time filter was applied. Only articles in English were evaluated. Synthetic description of included articles is reported in Table 1, whilst papers considered more relevant were deeply discussed in the text.

## Results

### Automatic reminder/recall

One of the benefits of IIS is the potential for generating automatic reminders or recalls. This review identified 21 articles

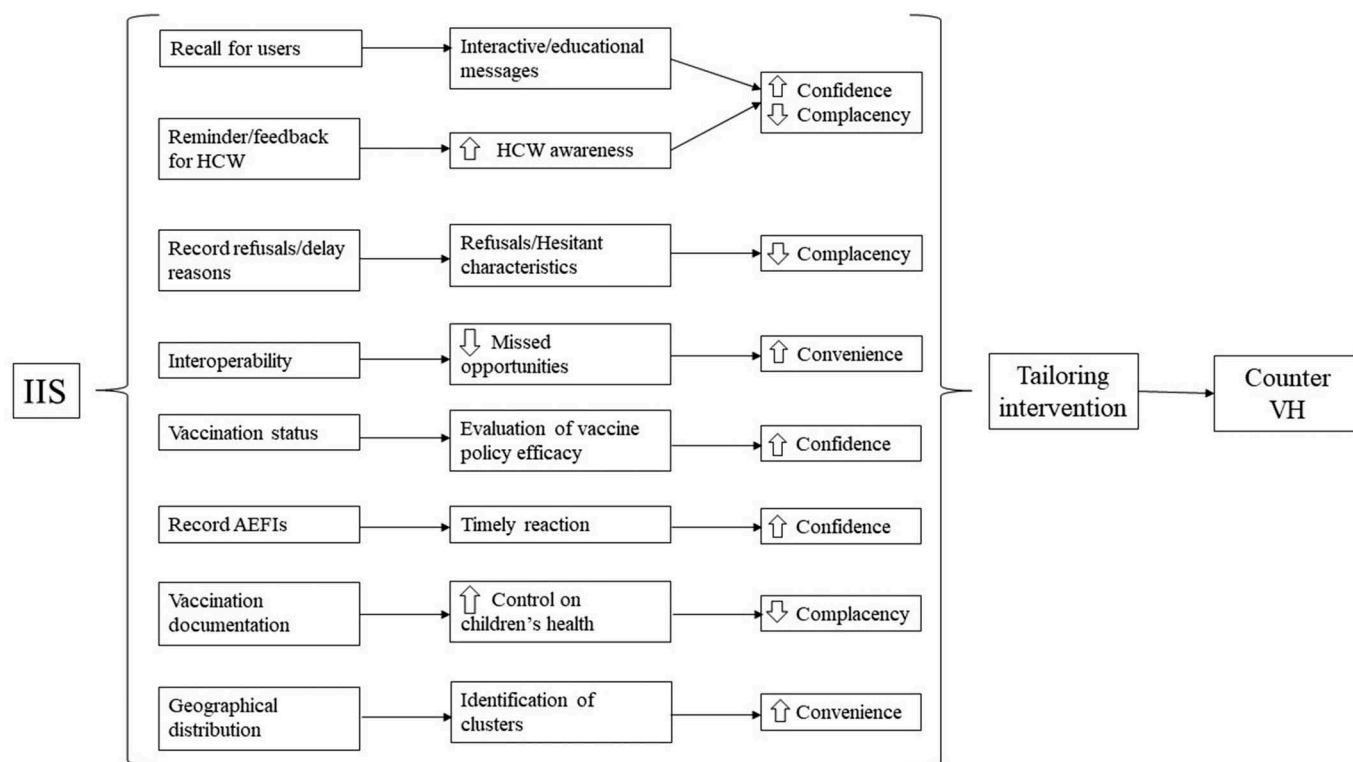


Figure 1. Conceptual framework for the use of IIS to counter vaccine hesitancy, according to the 3C model.

focused on reminder/recall and the IIS. Usually, the reminder/recall is developed to provide information about vaccination delivery, such as vaccines recommended or mandated for a child at a specific age and, in some cases, educational information is also provided.<sup>17–34</sup> Nowadays, many IISs are developed with a built-in reminder system that automatically emits reminders. These automated systems can send reminders directly to people who are in due for a vaccination, or otherwise, other automatic feedback/reminders are sent to health professionals, in order to be updated on the patients who have to be called for the next vaccination.<sup>13</sup> In 2012, IIS was used, for the first time, as a tool able to evaluate the efficacy of two different methods of reminders (paper mail plus text messages versus paper mail).<sup>32</sup> Indeed, researchers developed a text-messaging platform integrated with the IIS aimed to estimate the list of persons to be contacted. At the end of the study (January–June 2009), 21.8% of the patients who received text messages compared to 9.2% ( $p = 0.02$ ) who received only a letter were vaccinated. The same results were also obtained by Morris et al., who compared four different types of recall: postcard, text message, e-mail, phone call and nonintervention control group.<sup>29</sup> In this trial, the group who received a text message was the group with the highest rate of vaccination attendance (32.1% compared to 9.7% in the nonintervention group). Moreover, text message appeared to be the most effective system: fewer days passed between the reminder and when people were vaccinated (110 d compared to 234 d for nonintervention control).

Given the utility of a text-message reminder, the impact of (1) an educational and interactive text message, (2) educational only text-message reminder and (3) usual protocol (telephone appointment reminder with general information on vaccination)

on flu vaccine coverage in children (aged 6 months–17 y) who were not vaccinated until mid-November 2011<sup>26</sup> was also compared. The results proved the beneficial effect of text messages, especially the educational plus interactive text message ( $p < 0.02$  compared to usual care and  $p = 0.04$  compared to only educative text message). The possible explanation, as the authors suggested is that the interactivity increased the sense of responsibility due to the parents' active engagement that, in the 3C model, is represented by complacency. The text messages were sent by a platform, named EzVac, connected to the IIS. The IIS was also used to check the vaccination status and the timeliness of vaccinations. Recently, Suh and colleagues showed the greater adherence and cost-effectiveness of the recalls generated automatically from the centralized IIS compared to population-based recalls.<sup>34</sup>

These results highlight how new technology such as text messages and IIS can improve vaccine coverage, especially if mobile phone numbers are recorded as a part of the registration process and if the IIS is connected to the civil registry.<sup>132</sup> This last option could serve as a way to geo-localize patients and to send them a more tailored messaging reminder, for example, messages with information on where and when they can be vaccinated or how to receive more information. These functionalities can contrast VH by increasing convenience. Indeed, according to the 3C model, providing information on the vaccination delivery might influence convenience due to an increased perceived quality of services. Clark et al. conducted a cross-sectional web-based national survey of parents of children 0–17 y old, evaluating the experiences and preferences about reminder/recall immunization messages.<sup>18</sup> They found that 76% of parents received vaccination notices by mail, by e-mail and call to mobile phone and

**Table 1.** Characteristics extracted from the included studies.

Reference	Country	Name of IIS	Study aim	Main results
<i>IIS functionality explored: recall</i>				
Chung <sup>17</sup>	USA	North Carolina Immunization Registry	Evaluate the efficacy of registry-driven recall	VC was higher in intervention counties compared to the control
Clark <sup>18</sup>	USA	Michigan IIS	Evaluate parental's experiences and preferences about reminder/recall	56% of parents preferred to register their cell phone number and to receive call or text messages
Crawford <sup>19</sup>	Australia	Australian Childhood Immunisation Register	Evaluate the effect of post card recall on VC	The post card recall did not increase significantly the VC
Custis <sup>20</sup>	USA	WIZRD	Evaluate the effect of recall letter on VC	The recall letter did not increase significantly the VC
Dombkowski <sup>21</sup>	USA	Michigan Care Improvement Registry	Assess feasibility for initiating a recall by private sector	The cost of recall intervention ranged between \$0.05 and \$6 per children
Dombkowski <sup>22</sup>	USA	Michigan Care Improvement Registry	Evaluate the feasibility and effectiveness of recall during seasonal flu campaign	Recall group had a VC significantly higher compared to the control group
Dombkowski <sup>23</sup>	USA	Michigan Care Improvement Registry	Assess the completeness of parent contact information	Adolescents had the lowest data completeness
Dombkowski <sup>24</sup>	USA	Michigan Care Improvement Registry	Evaluate the effect of centralized recall strategies on children VC	Children 19 months old in the recall group had significantly higher immunization activity compared to children who did not receive a recall notification
Dombkowski <sup>25</sup>	USA	Michigan Care Improvement Registry	Evaluate the effect of recall strategies for flu vaccination, among chronic children	The recall strategy increased significantly the VC among intervention group compared to control
Hofstetter <sup>26</sup>	USA	New York State IIS	Determine the impact of text message on flu VC among unvaccinated children	Beneficial effect of educational plus interactive text message on VC
Kempe <sup>27</sup>	USA	Colorado IIS	Compared population-based recall vs. practice-based recall	Population-based recall was more effective and cost-effective
Kempe <sup>28</sup>	USA	Colorado IIS	Compared collaborative centralized vs. practice-based recall approaches	The centralized recall was more cost-effective compared to practice-based (\$11.75 vs. \$74.00 per child, and vaccination was performed in 19.2% vs. 9.8% of children)
Morris <sup>29</sup>	USA	San Diego Immunization Registry	Compare 4 types of recall: postcard, text message, e-mail, phone call and nonintervention control group	The text message group had the highest VC
Saville <sup>30</sup>	USA	Colorado IIS	Identify parents' preferences on type of recall	The most preferred recall was mail, followed by telephone, e-mail and lastly messages
Stockwell <sup>31</sup>	USA	New York Citywide Immunization Registry	Evaluate the effect of educational recall messages	Children and adolescents who received the recall had higher VC compared to control
Stockwell <sup>32</sup>	USA	New York Citywide Immunization Registry	Evaluate the efficacy of two types of recall (paper mail plus text messages vs. paper mail)	Text-messaging platform integrated with the IIS was developed and users who received text messages had higher VC
Stockwell <sup>33</sup>	USA	New York Citywide Immunization Registry	Evaluate the efficacy of recall on health record	The recall increased documentation of the reason for vaccine non-administration
Suh <sup>34</sup>	USA	Computerized immunization registry in Denver Community Health Services	Estimate the effectiveness of automatic recalls	The intervention group had significantly higher VC for at least one vaccine and for all targeted vaccines
<i>IIS functionality explored: reminder</i>				
Allison <sup>35</sup>	USA	Regional IIS	Evaluate the effectiveness of a reminder for flu seasonal vaccine in chronic patients	VC in chronic patients did not change during the study period. However, the VC in healthy children reduced
Brousseau <sup>36</sup>	Canada	Vaccination registry VAXIN	Evaluate the impact of feedback to immunization providers	Provide feedback to vaccinators, promoted a changes in immunization providers' habits
Crawford <sup>37</sup>	Australia	Australian Childhood Immunisation Register	Evaluate the effectiveness of an audit findings feedback	Reminder improved vaccine delivery
<i>IIS functionality explored: characteristics of vaccine refusers and vaccine recipients</i>				
Beard <sup>38</sup>	Australia	Australian Childhood Immunisation Register	Evaluate the trend of vaccination objections	The objections recorded increased over the time. Children resident in low SES area had the higher rate of vaccination objections
Bernhardt <sup>39</sup>	New Zealand	New Zealand National Immunisation Register	Explore association between vitamin K prophylaxis decline and low acceptance of vaccination	Refusing vitamin K prophylaxis was associated with low acceptance of vaccinations
Feemster <sup>40</sup>	USA	Vaccines for Children program database	Identify characteristics of children who delay vaccination	Maternal characteristics and type of prenatal care visits were associated with vaccines delay
Feiring <sup>41</sup>	Norway	Norwegian Immunisation Registry	Identify reasons to not accept HPV vaccination	Parental education and income were associated with HPV vaccine acceptance
Forbes <sup>7</sup>	Australia	Australian Childhood Immunisation Register	Evaluate the vaccination uptake after immunization consultation among hesitant parents	42% of hesitant parents accepted the vaccination after the consultation
Gold <sup>42</sup>	USA	Oregon's IIS	Evaluate timing of HPV vaccination	Age and ethnicity were associated with timely and completion of vaccination
Gowda <sup>43</sup>	USA	Michigan Care Improvement Registry	Identify factors associated to vaccination acceptance	Age, provider type and childhood immunization history were factors associated with vaccination acceptance
Grant <sup>44</sup>	New Zealand	New Zealand National Immunisation Register	Identify antenatal factors associated to vaccination acceptance	Addressing vaccine concerns during antenatal periods increases vaccination acceptance

(Continued)

Table 1. (Continued).

Reference	Country	Name of IIS	Study aim	Main results
Gupta <sup>45</sup>	USA	Virginia's Statewide IIS	Identify factors associated to vaccination acceptance	Access limitations, perception of low urgency and safety of vaccine were main factors
Hofstetter <sup>46</sup>	USA	New York State Citywide IIS	Identify characteristics of children who performed vaccination in time	Missed opportunities and ethnicity were negatively associated with timeliness
Lin <sup>47</sup>	China	China Information Management System for Immunization Programming	Identify factors associated with measles vaccination delay	Immigration, sex, low SES, had a history of delays in other vaccinations and had parents who did not believe in vaccinations importance were determinants of measles vaccination delay
MacDonald <sup>48</sup>	Canada	Canadian Regional Immunization Registry	Identify reasons for partial immunization	Safety concern, lack of awareness and lack of trust in the health institutions were the most frequent reasons for partial immunizations
Martinez-Baz <sup>49</sup>	Spain	Population-based vaccination registry	Analyze factors influencing continued adherence to flu vaccination	Number of physician visits per year, sex, age and major chronic condition were statistically associated with flu vaccination
Nadeau <sup>50</sup>	USA	New York State IIS	Evaluation of trends in alternative schedule compliance	Alternative schedule was mainly adopted by children not up-to-date at age 9 months, with 2 extra vaccine visits compared to children following standard schedules
Riise <sup>51</sup>	Norway	Norwegian Immunisation Registry SYSVAK	Identify characteristic of children delaying vaccinations	Be an immigrant children, vaccinations scheduled during summer and first dose of measles had the higher odds to delay vaccination
Robison <sup>52</sup>	USA	Oregon ALERT IIS	Evaluation of trends in alternative schedule compliance	Alternative schedule was increasingly adopted during the study period
Schmitt <sup>53</sup>	USA	Florida statewide immunization registry	Examine factors associated with HPV immunization timely completion	Women under Medicaid were less likely to complete the vaccination on time, as African-Americans, and aged 18–21
Tan <sup>54</sup>	USA	North Caroline Immunization Registry	Assess characteristic of girls in time with the HPV vaccination	Ethnicity and race, such as having received previous vaccine doses in time, were associated to receive HPV vaccine doses on time
Van Keulen <sup>55</sup>	Netherlands	Dutch national immunization register Præventis	Evaluate the factors related to HPV vaccination acceptance	Social-psychological variables largely impacted on HPV vaccination acceptance
van Lier <sup>56</sup>	Netherlands	Dutch national immunization register Præventis	Identify uptake vaccine determinants	Low VC was associated with had at least one parent born out of the Netherlands and low SES
Wagner <sup>57</sup>	United Kingdom	CHIS	Monitoring vaccination coverage by ethnicity	Ethnicity but not deprivation was associated with VC. Practitioner not in practice in the CHIS decreased the odd to be vaccinated
Wei <sup>58</sup>	USA	Vaccine Safety Datalink	Assess refusal status	Racial, education and income characteristics were associated with vaccinations refuse
Wilson <sup>59</sup>	Canada	Immunization Records Information System	Evaluate the trend of nonmedical expectations	Religious/Conscientious exemptions increased over the study period
Wilson <sup>60</sup>	Canada	Immunization Records Information System	Evaluate the trend of nonmedical expectations	Nonmedical exemptions increased over the period
Woestenber <sup>61</sup>	Netherlands	Dutch national immunization register Præventis	Estimate the timeliness vaccination among preterm infants	Urbanity, being vaccinated in hospital, ethnicity, gestational age and birth weight impact on vaccination timeliness
<i>IIS functionality explored: missed opportunities</i>				
Berling <sup>62</sup>	Australia	Australian Childhood Immunisation Register	Estimate missed opportunities in local ED	35/95 cases were missed opportunities
Daley <sup>63</sup>	USA	Regional IIS	Assess frequency of missed opportunities	Missed opportunities occurred approximately in 70% of all vaccine-eligible visits
Oltean <sup>64</sup>	USA	Washington State IIS	Estimate missed opportunities for HPV	One-third of eligible unvaccinated girls and two of five eligible boys aged 11–17 y had at least one missed opportunity to receive HPV
Shingle <sup>65</sup>	New Zealand	New Zealand National Immunisation Register	Evaluate the effectiveness of an audit of missed opportunities	The majority of children under immunized were vaccinated in hospital setting
Verani <sup>66</sup>	USA	New York State IIS	Assess the prevalence of missed opportunities	Missed opportunities had occurred in 82.2% of all vaccine-eligible visits
Way <sup>67</sup>	Australia	Australian Childhood Immunisation Register	Estimate the proportion of missed opportunities in ED	Half of the children overdue for immunization remained under immunized for more than 77 d in mean
<i>IIS functionality explored: interoperability and DSS</i>				
Hosseini <sup>68</sup>	Iran	Iran's IIS	Simplify and encourage the use of decision system support within the IIS	Address interoperability within and between IISs
Rajamani <sup>69</sup>	USA	Minnesota Immunization Information Connection	Evaluate the utilization of DSS for immunizations	59% of queries identified a successful record
Stevens <sup>70</sup>	USA	California Immunization Registry	Develop an integrated interface between IIS and EMR	The new interface was considered more comfortable and efficient by physicians
Swenson <sup>71</sup>	USA	Regional IIS	Evaluate the effect of DSS on VC	DSS identified more patients increasing VC among adults
<i>IIS functionality explored: vaccine program performance</i>				
Ali <sup>72</sup>	Australia	Australian Childhood Immunisation Register	Evaluate if visiting practices with low VC increase the immunization rate	The intervention increase the VC
Brotherton <sup>73</sup>	Australia	Australian National HPV Vaccination Program Register	Evaluate the efficacy of a school-based approach	70% of girls in this age group was fully vaccinated

(Continued)

Table 1. (Continued).

Reference	Country	Name of IIS	Study aim	Main results
Cates <sup>74</sup>	USA	Sentinel IIS sites	Evaluate the effect of a social marketing intervention to increase HPV VC	VC increased by 34%
Clayton <sup>75</sup>	USA	Michigan Care Improvement Registry	Evaluate the effect of immunization provider type	Public providers had lower odds of vaccinating children compared to private
Ernst <sup>76</sup>	USA	Arizona State IIS	Evaluate the effect of new policy on HAV VC	Differences were found among the regions with different policies implemented
Feiring <sup>77</sup>	Norway	Norwegian Immunisation Registry	Efficacy of selective immunization strategy	Selective vaccination reached lower rate of VC compared to universal program
Hull <sup>78</sup>	Australia	Australian Childhood Immunisation Register	Evaluate the impact of introduction of new vaccine (rotavirus)	Timeliness of other vaccinations improve
Humiston <sup>79</sup>	USA	New York State Citywide IIS	Evaluate the impact of SLV influenza programs	Intervention group had higher VC compared to control group
Isaac <sup>80</sup>	Canada	Manitoba IIS	Evaluate the efficacy of home visiting programs on VC	VC increased among families enrolled in the home visiting program compared to controls
Kansagra <sup>81</sup>	USA	New York State Citywide IIS	Evaluate the impact of SLV influenza programs to reach children never immunized against flu	SLV reach more children never immunized
Kharbanda <sup>82</sup>	USA	New York State Citywide IIS	Evaluate VC changes after the introduction of school mandated immunization	VC increased during the study period
Melinkovich <sup>83</sup>	USA	Computerized immunization registry in Denver Community Health Services	Evaluate VC after implementation of combined several types of activities	Financial incentives and shared strategy and policy increased VC
Moore <sup>84</sup>	Australia	Australian Childhood Immunisation Register	Evaluate the effect of policy initiatives on VC	Proactive follow up of children, more sustain for immunization services and centralization of vaccine delivery service increased VC
Moss <sup>85</sup>	USA	North Carolina Immunization Registry	Analyze organization aspects of clinics that impact on vaccination acceptance	Pediatrics clinics specializing in pediatrics had higher VC for pediatrics vaccines but not for HPV, also vaccination documentation type impact on VC
Moss <sup>86</sup>	USA	North Carolina Immunization Registry	Evaluate the efficacy of a brief intervention on HPV VC	The intervention (webinar) increased VC during the study period
Potter <sup>87</sup>	USA	Michigan Care Improvement Registry	Evaluate the effect of new school rules and vaccine coadministration	The new policy was associated with high completion rate of the vaccines required
Rehn <sup>88</sup>	Sweden	Swedish vaccination register SVEVAC	Evaluate the efficacy of implementation strategies	Counties offering vaccination in school had higher VC compared to counties without vaccination program in school
Simpson <sup>89</sup>	USA	Arizona State IIS	Evaluate the VC changes after the school entry mandate	After the school entry mandate the VC increased
Sull <sup>90</sup>	USA	New York State Citywide IIS	Estimate the effect of vaccine coadministration on VC	Age-specific VC increased
Suryadevara <sup>91</sup>	USA	New York State IIS	Estimate the efficacy of multicomponent community-based interventions	VC increased after providing practical information about where, why and how to perform vaccinations
Teplow- Phipps <sup>92</sup>	USA	New York State Citywide IIS	Identify factors associated with early uptake and completeness of immunization	Greater odds of early uptake were registered among publicly insured adolescents, while completion was higher in private hospital
Ward <sup>93</sup>	Australia	Australian Childhood Immunisation Register	Evaluation of varicella vaccination program implementation	The introduction of public-funded vaccination increased VC in 24 months aged children, but not in adolescents
<i>IIS functionality explored: record or link AEFIs data</i>				
Alguacil-Ramos <sup>94</sup>	Spain	Vaccination Information System	Estimate the incidence of AEFIs	An increased number of AEFIs were recorded after the switch from DTaP to Tdap
Arnheim-Dahlstrom <sup>137</sup>	Sweden	Swedish vaccination register SVEVAC	Evaluate incidence of epileptic seizures after A/H1N1 vaccination	No association between epileptic seizures and flu vaccination
Baker <sup>95</sup>	USA	Florida, Michigan, Minnesota, New York, Pennsylvania, Wisconsin and Virginia IIS	Merge data from different database to evaluate the efficacy of a post-licensure vaccine safety program (PRISM)	The PRISM was complete enough to guaranty a valid surveillance system
Bakken <sup>96</sup>	Norway	Norwegian Immunisation Register	Estimate the risk of febrile seizure after flu infection or vaccination (A/H1N1)	The risk of febrile seizure was higher in both group
Buttery <sup>97</sup>	Australia	Australian Childhood Immunisation Register	Evaluate the risk of intussusception after rotavirus vaccination	No significant increased risk of intussusception, but there was some evidence of higher risk following the first dose
Carlin <sup>98</sup>	Australia	Australian Childhood Immunisation Register	Evaluate the risk of intussusception after rotavirus (Rotarix and RotaTeq) vaccination	Similar increased risk after both types of vaccine; however, the benefits were higher compared to the risk
Conlin <sup>99</sup>	USA	The National Smallpox Vaccine in Pregnancy Registry	Evaluate the risk of pregnancy loss after inadvertently smallpox and/or anthrax vaccination	No risk after inadvertently smallpox and/or anthrax vaccination during pregnancy
De Wals <sup>100</sup>	Canada	Meningococcal Vaccination Registry	Analyze mortality after meningococcal C vaccination	Mortality rate for all causes was higher in the control group
Dey <sup>101</sup>	Australia	Australian Childhood Immunisation Register	Identify a proxy for an early-onset AEFIs	Representation to general practice, 48 h after immunization, is a good proxy of early-onset AEFIs

(Continued)

Table 1. (Continued).

Reference	Country	Name of IIS	Study aim	Main results
Gold <sup>102</sup>	Australia	Australian Childhood Immunisation Register	Evaluate the association between MMR vaccination and febrile convulsion	Confirmation of association between MMR vaccination and febrile convulsion
Håberg <sup>103</sup>	Norway	Norwegian Immunisation Register	Evaluate the risk of fetal death after flu vaccination during pregnancy	No association between flu vaccination in pregnancy and fetal death was associated. Fetal death was higher after flu infection in pregnancy
Heier <sup>104</sup>	Norway	Norwegian Immunisation Register	Estimate the risk of narcolepsy after A/H1N1 vaccination	Risk of narcolepsy was higher in children 4–19 y old
Hu <sup>105</sup>	China	Individual IIS	Describe the reported AEFIs	The majority of AEFIs recorded were nonserious events
Kiraly <sup>106</sup>	Australia	Australian Childhood Immunisation Register	Estimate the risk of allergy after DTaP vaccination	No increased risk of atopy was found
Liang <sup>107</sup>	China	National IIS's National Adverse Event Following Immunization Surveillance System	Assess the post-marketing safety of flu vaccination	No patterns of AEFIs were identified
Liu <sup>108</sup>	Canada	Alberta Immunization and Adverse Reaction to Immunization	Estimate the incidence of AEFIs and venous thromboembolism, after HPV vaccination	Incidence of AEFIs was within the expected rate
Lloyd-Johnsen <sup>109</sup>	Australia	Australian Childhood Immunisation Register	Estimate the incidence of intussusception after rotavirus vaccination among patients admitted to the Royal Children's Hospital	Intussusception after vaccination occurred in 27 patients admitted to the Royal Children's Hospital
Macartney <sup>110</sup>	Australia	Australian Childhood Immunisation Register	Evaluate the association between MMR and varicella vaccination and febrile convulsion	There was an association between MMR vaccination and febrile convulsion, but not for varicella vaccine
Persson <sup>111</sup>	Sweden	Swedish vaccination register SVEVAC	Evaluate the risk of neurological and immune-related diseases after A/H1N1 vaccination	Increased risk of narcolepsy in subjects younger than 20 y old
Rouleau <sup>112</sup>	Canada	Provincial Pandemic Influenza Vaccination Registry	Identify risk factors associated with anaphylaxis after flu pandemic vaccination	Women with acute respiratory infection or food allergy had higher risk of anaphylaxis
Rousseau <sup>113</sup>	Canada	Québec BCG Vaccination Registry	Evaluate the association between BCG vaccine and diabetes	No association was found
Schurink-van <sup>114</sup>	Netherlands	Dutch national immunization register Præventis	Estimate the risk of migraine after HPV vaccination	No association was found
Stehr-Green <sup>115</sup>	New Zealand	New Zealand National Immunisation Register	Estimate the risk of bronchiolitis after meningococcal B vaccination	No association was found
Van Der Maas <sup>116</sup>	Netherlands	Dutch national immunization register Præventis	Identify potential AEFIs after HPV vaccination	No severe AEFIs were found, neither venous thromboembolic events
<i>IIS functionality explored: social mobilization</i>				
Robison <sup>117</sup>	USA	Oregon ALERT Immunization Information System	Produce more accurate VC rate among adolescents, weighting individual records by the length of time since last activity	Weighting individual records improved the fit of IIS data
Wilson <sup>118</sup>	Canada	Immunization Records Information System	Assess mobile phone software as a tool to solve the issue of people's mobility	Mobile technologies can empower individuals with their own health information
<i>IIS functionality explored: identify barriers</i>				
Charland <sup>119</sup>	Canada	Montreal IIS	Identify barriers for under-immunization	Ethnic-religious barriers and socioeconomic barriers such as poverty, immigrant status, high residential density, material deprivation and high violent crime rates impacted on VC
Fu <sup>120</sup>	USA	Washington, IIS	Evaluation of spatial accessibility and vaccination compliance	Having high level of access to pediatric vaccination providers is associated with high vaccination compliance
Hull <sup>121</sup>	Australia	Australian Childhood Immunisation Register	Estimate the 7vPCV coverage in Aboriginal	VC vary significantly between the very remote areas and the accessible districts
Hull <sup>122</sup>	Australia	Australian Childhood Immunisation Register	Evaluate factors associated with vaccination timeliness	Timeliness is negatively associated with age, remoteness and later doses of vaccine
<i>IIS functionality explored: geographical distribution</i>				
Barbaro <sup>123</sup>	Australia	National HPV Vaccination Program Register	Geographic distribution of HPV VC	VC in low SES areas was lower than in high SES areas
Brien <sup>124</sup>	Canada	Immunization Records Information System	Geographic distribution of VC	VC in low SES areas was lower than in high SES areas
Eccles <sup>125</sup>	Canada	Immunization Records Information System	Geospatial distribution of MMR vaccination	Clusters of high immunization rates in the center compared to low rate in south and north
Mueller <sup>126</sup>	New Zealand	New Zealand National Immunisation Register	Identify geographical distribution and disparities in immunization uptake	Ethnicity, low SES, year of birth and geographic location were associated with low immunization
Teng <sup>127</sup>	Haiti	Electronic immunization system developed ad hoc	Monitor the vaccination campaign after cholera outbreak in Haiti	Identification of geographical distribution of community coverage
Thompson <sup>128</sup>	USA	Florida Department of Health IIS	Identify geographical distribution after the outbreak of measles	It was possible to map the percent of children with religious exemptions, children on track or overdue for each vaccine series and children with no recorded vaccine

(Continued)



Table 1. (Continued).

Reference	Country	Name of IIS	Study aim	Main results
Trogdon <sup>129</sup>	USA	North Carolina Immunization Registry	Evaluate spatial patterns in HPV vaccination acceptance	Identification of underimmunized cluster that were low public-funded areas
Trogdon <sup>130</sup>	USA	North Carolina Immunization Registry	Evaluate spatial patterns in flu vaccination acceptance	Underimmunized cluster were in low public-funded areas
Wagner <sup>131</sup>	China	Shanghai Immunization Program Information System	Evaluate the effect of urbanity on VC	Disparities were higher in migrant population compared to locals, and it was higher in suburb areas

HCW: Health-care worker; VH: vaccine hesitancy; IIS: immunization information system; AEFIs: adverse events following immunizations; HPV: human papilloma virus; VC: vaccination coverage; SES: socioeconomic status; ED: emergency department; EMR: electronic medical records; SLV: school-located vaccination; MMR: measles, mumps, rubella; HAV: hepatitis A virus; DSS: decision support systems; BCG: Bacillus Calmette–Guérin; WIZARD: web-based immunization registry database; CHIS: child health information systems.

that none received a text message. However, only 33% of the parents preferred to still receive notices by mail, while 3% preferred to receive text messages, and 56% of parents indicated that they would be willing to register their cell phone number to receive future call or text messages with information regarding immunization. The IIS could be a useful tool to record parental preferences about reminder/recall message modes. In general, the new technologies could help to increase parental empowerment regarding child vaccination, thanks to educational and tailored text messages, based on the characteristics of child, vaccinations and doses. However, to better understand text messaging, the methodologies and the applicability of this innovative system, other studies are ongoing.<sup>133</sup> In particular, we expect future studies on the application of social software (e.g., WhatsApp) that could represent the next and cheaper strategy compared to the text messages.

Usually, this reminder/recall approach is designed for the user but several studies evaluate the possibility to also send a reminder to the HCW.<sup>35–37</sup> This particular type of feedback/reminder is based on the vaccine coverage data and on the best evidence-based practice. Different organizational models are in place in different countries; however, the main advantage is that HCW can personalize immunization care, tailor counseling and lastly move from administrative to involvement tasks. Brousseau and colleagues demonstrated how providing feedback to vaccinators is an effective strategy to improve vaccine coverage and reduce vaccine delay.<sup>36</sup> In this study, IIS was used to identify the clinics that had administered the highest number of doses of DTaP–polio–Hib, pneumococcal, meningococcal and mumps, measles and rubella (MMR) in 2007 in Quebec City, to calculate the vaccine coverage rate before and after the intervention and to establish the number of vaccination delays. During the two feedback sessions (before and after the intervention), authors presented the coverage data, the vaccine delays data obtained for the previous years and the best evidence practice; moreover, they also surveyed the organizational characteristic of the clinics. After a 12-month period, they found an increased number of administered doses and an increase in proportion of vaccines administered in time. A statistically significant increase was observed for DTaP–polio–Hib and pneumococcal (both +9%  $p < 0.001$ ) using the 1-week delay definition. No significant statistics were observed for the 1-month definition. Moreover, after the intervention (provide feedback to vaccinators), four of the ten respondent clinics changed their habits, encouraging multiple injections and two of them improved nurse contribution. Among these four clinics, the vaccine delay was significantly decreased. The increasing

proportion of infants immunized within a 1-month delay ranged from 32% to 44.6% ( $p < 0.001$ ) for pneumococcal vaccine. The proportion of infants immunized without delay for MMR increased from 27.4% to 67.6% ( $p < 0.001$ ) and from 56.5% to 80.9% ( $p < 0.001$ ) for meningococcal.

Finally, these data highlight the important role played by IIS in vaccination reminders both to parent/patients and to HCW. Indeed, with educational text messages, parents can improve their empowerment on vaccination and are also facilitated with respect to the immunization schedule, while HCW can update, in real time, the immunization status of their patients. This shows that IIS could counteract VH by increasing the number of opportunities during which hesitant parents could discuss immunization with professionals. According to the 3C model, this could be beneficial to increase confidence and to contrast complacency.

### Characteristics of vaccine refusers and vaccine recipients

Several recent reports confirm that the “new” outbreaks of measles and pertussis, for example, start in unvaccinated individuals and then spread to children whose vaccination may have failed. Due to these fundamental public health issues and the decreased immunization coverage, it is extremely important to know refusal and recipients characteristics. We identified 25 papers aimed to explore the characteristics of refusal or recipients.<sup>7,38–61</sup> Wei and colleagues used the information from the IIS to assess refusal status and then retrieved the racial, education and income characteristics from the census tract.<sup>58</sup> In this study, refusers had higher education levels and incomes  $p < 0.03$  compared to non-refusers. Moreover, the refusers had no well-child visit and, compared to non-refusers, a higher percentage of refusers took antibiotics or seizure medications ( $p = 0.0003$ ).

Van Lier and colleagues, using IIS, were able to outline the incomplete vaccination status of children in the Netherlands. The partially immunized children had at least one parent born out of the Netherlands or in no Western country; even a low socioeconomic status was associated with low vaccination coverage.<sup>56</sup> Another example comes from the study by MacDonald et al. where they assess, through a postal questionnaire, the reasons for no vaccination, or partial immunization, in children 2 y old during the period May 2008–April 2009 in Edmonton, Canada.<sup>48</sup> The obtained results show that concerns about vaccine safety, lack of awareness about disease severity and susceptibility and lack of trust in

the health institutions and government were the most frequent reasons for partial immunizations, whereas children attending day care who had regular contact with a pediatrician and had at least one parent working outside the home were the most likely to complete the vaccinations. From these studies, it is noticeable how IIS might resolve the issue related to identification of unvaccinated people, especially if vaccine refusals are recorded as a part of the registration process and if the IIS is connected to pediatricians or family doctors' software (electronic medical record systems). This function of IIS, if concretely used, could be important to contrast "complacency", because it could allow analysis of parents' reluctance.

Moreover, IISs may allow to record parents' reasons of vaccinations refusal. Beard et al. published in 2016 a study evaluating the trend of vaccination objections.<sup>38</sup> People more affected by vaccine objections were the groups aged 12 months to 7 y old, in the lowest 10% of postcodes regarding socioeconomic status, while children born overseas had less registered objections.

Health programs rarely have the ability to track and follow-up vaccination refusers. It may seem to be expensive and time consuming but previous epidemiological studies have shown that refusers are able to transmit diseases to vaccinated individuals (taking into account vaccine efficacy and full immunization of people) when the two groups are mixed in a crowded area. Also Italy, with a subnational IIS – a national IIS, in Italy, is currently establishing<sup>134</sup> – was able to analyze reason of vaccinations refusal.<sup>135</sup> The IIS can provide the needed fundamentals to record the refusal status and the reasons for refusal.

Through IIS, it could also be possible to study the profile of people vaccinated and the characteristics of those who complete vaccination on time. Martinez-Baz et al., using a population-based vaccination registry (IIS), evaluated the proportion of persons vaccinated against influenza in Navarre, Spain, in the 2010–2011 season.<sup>49</sup> The aim was to analyze the factors influencing continued adherence to influenza vaccination in people older than 65 y and in those with major chronic conditions, who are considered at high risk of influenza complications.

Tan et al. extrapolated immunization records from the North Carolina Immunization Registry (their IIS) to evaluate the characteristics of girls who completed the HPV vaccination and completed it on time.<sup>54</sup> They stratified for several sociodemographic characteristics and they found that ethnicity and race was one of the most important factors influencing the completeness and on time delivery of the vaccine doses (59% vs. 43%  $p < 0.001$  white vs. black, 51% vs. 47%  $p < 0.001$  non-Hispanic vs. Hispanic for both completeness and on time). Comparing the funding type, those whose vaccine was privately funded were more likely than those that were publicly funded to complete the vaccine schedule and do it on time (both  $p < 0.001$ ). Approximately 50% of those who completed the vaccination on time were immunized at pediatrician, GP clinics or local health units (both  $p < 0.001$ ).

Leveraging IIS is possible to define the characteristics of vaccines refusers, which is extremely important in order to tailor the vaccination campaign. It is particularly true if we look at the parents' fear on vaccine safety. Clearly, the opportunity to understand better the characteristics of target

population depends on the type and quality of data recorded. Geographic or demographic data, such as reasons for not vaccinated, could not be available in all IISs.

### **Interoperability, missed opportunities and decision support system**

One of the possible reasons for a low specific vaccine rate is missed opportunities; through this review, six manuscripts were retrieved and analyzed.<sup>62–67</sup> Verani and colleagues performed a retrospective evaluation of 2001–2005 influenza seasons (using data from New York Citywide Immunization Registry) aimed to assess the prevalence of missed opportunities in children aged 6–23 months, among a practice network in New York.<sup>66</sup> Missed opportunities were defined as clinic visits during which the patients eligible for vaccination did not received vaccine. Missed opportunities had occurred in 82.2% of all vaccine-eligible visits, but with a remarkable decrease during the 5 y of study that was followed by an increasing coverage rate. Daley et al. conducted a prospective cohort study evaluating the frequency, reasons and the characteristics of missed opportunities for flu vaccinations in children aged 6–72 months with high-risk conditions, among four pediatrics clinics in Denver, during the 2002–2003 influenza season.<sup>63</sup> They extracted the vaccination status from the IIS, and the information about number, reasons and characteristics of clinical visits from billing databases. Also in this study, the missed opportunities were around 80%. Daley et al. surveyed parents of unvaccinated children to understand the reasons for no immunization. In the majority of the cases (29%), the reason was lack of physician recommendation, followed by low perception of flu risk (23%) and lack of particular reason (24%), while 13% were worried about potential vaccination risk. Only in 6% of cases was there a real opposition to the vaccinations, while in 5% of the cases, the reason was parental barriers. We can see that, probably, around 89% of unvaccinated children could have been immunized if they had received recommendations, information and education on vaccines. The missed opportunities for flu vaccine are particularly high, and interoperability between IIS and GP software, for instance, might reduce these occurrences. In fact, it is plausible that physicians can fail to recommend immunizations if they are not aware of both vaccination status or vaccine indications for their patients. Having this information available might increase the number of occasions in which HCW and parents can deal with the issue of vaccinations, addressing parents' doubts and insecurities and thus reducing VH. Indeed, offering tailored counseling is extremely important in countering VH. Interoperability and DSS are extremely important for this aspect, as reported in the four articles found in the literature.<sup>68–71</sup> Steven and colleagues present a brilliant example of bidirectional interface between electronic medical records and IIS. They developed a visual integrated interface by which physicians could easily and quickly acquire patients' immunization information directly from IIS.<sup>70</sup> Of surveyed physicians, 68% feel more comfortable with the new interface; furthermore, they consider it much more efficient. IIS might provide decision support to the physician or to those who perform vaccinations, and assessment or feedback automatically generated can reduce missed opportunities. Hosseini and colleagues developed a method able to address interoperability within

and between IISs; moreover, their main aim was to simplify and encourage the use of decision system support within the IIS.<sup>68</sup> Recently, Martinelli and colleagues combined three different data sources (hospital discharge registry, drug prescription registry and user fee exempt registry) with the IIS to identify patients with chronic diseases eligible for vaccination.<sup>136</sup> All the IISs are more operational when they are comprehensive and largely used by HCW. The decision support system is crucial to help physicians during their work, improving adherence to clinical guidelines and to provide alerts or recommendations in case of needed precautions. IIS equipped with decision system support could reduce the missed opportunities and improve the quality of the service. This is important if we take into account the impact of IIS on “convenience”. At the same time, IIS with decision support might help physicians to increase their trust in their own institution, which can act on “confidence”. The lack of trust may be a contributing factor to the increase in VH also in HCW.

### ***IIS as an instrument to measure vaccine program performance***

The concerns of health policy makers about the growing phenomenon of VH force them to promote public health strategies within civil society and among HCW. IIS is a tested tool to evaluate the efficacy of vaccine policy through the assessment of changing vaccine coverage rates before and after policy intervention. Related to this topic, 22 manuscripts were included in this study.<sup>72–93</sup> Cates and colleagues assessed vaccine coverage after 3 months of social marketing experiments aimed to facilitate conversation among adolescents/parents and physicians about HPV vaccination.<sup>74</sup> They compared the data from IIS of two different counties (one where they performed the intervention and the other as a control) and the probability to get vaccinated was 34% higher in the intervention county. Isaac et al. consulted the Manitoba IIS to assess the efficacy of home visiting programs on vaccine coverage.<sup>80</sup> They found higher complete vaccinations in children aged 1–2 y in the families enrolled in the home visiting program compared to control. Grant and colleagues have shown that to address vaccine concerns during antenatal periods is the best method to improve the rate of parents agreeing with full immunization of their child.<sup>44</sup> They surveyed both pregnant women and their partners about the intentions of future infant immunization; then the child’s immunization status was assessed by IIS. The results show the highest proportion of timely vaccinations in children whose mother and partner were involved in the decision process; moreover, timeliness was also associated with a mother’s decision to fully immunize, independently of the mother’s demographics and partner’s intention. However, the timeliness was much higher if both mother and partner agreed with complete immunization. Nevertheless, 22% of partners versus 14% of pregnant women hadn’t decided about vaccinations, which might reflect the lesser partner engagement with physicians. Addressing parental concern through educational interventions is associated with increasing coverage rates.<sup>44</sup> Suryadevara et al. demonstrated the effectiveness of multicomponent community-based interventions in increasing vaccine coverage among poor families.<sup>91</sup> They performed a face-to-face

interview, investigating parental concern and at the same time providing practical information about where, why and how to perform vaccinations; additionally, they offered vaccines on site. Nine months after the intervention, the children with “vaccine-complete” status increased from 28% to 45%; in adolescents, the HPV vaccination had increased 16%, 8% for meningococcal vaccine. Finally, the flu vaccine had a 17% increase compared to 8% in one county (without intervention), during the same period.

Kharbanda et al. evaluated changes on coverage rates, before and after the introduction of school mandated immunization.<sup>82</sup> Data on immunization coverage were extracted from IIS (EzVAC: web-based immunization registry of New York). They evaluated the coverage rate of diphtheria and pertussis (Tdap) and meningitis (MCV4) (vaccines required by the mandate) in three overlapping cohorts of adolescents aged 11–14 y, in three consecutive years: pre mandate, the first year of mandate and the following year. Data show a remarkable increase of coverage rates for both vaccines, which was stunning throughout the study period (Tdap coverage moved from 29% in pre mandate era to 58% during the first year, to 83% during the following year. Data are also similar for MCV4). Also, Simpson and colleagues, through IIS, found an increasing coverage rate after changes in the school entry mandate, requiring meningococcal vaccinations for all 11–18 y old adolescents as CDC Advisory Committee on Immunization Practices recommended in 2007.<sup>89</sup>

### ***Possibility to record AEFI***

As a consequence of the high safety and efficacy vaccines, the perception of infectious disease severity is decreasing, conversely increasing vaccine concern. This scenario imposes an increase and renewal of surveillance strategies of adverse events after immunizations, especially in light of the introduction of newly licensed vaccines. The integration between IIS and the AEFI registry can be important to identify new and rare adverse reactions, to recognize new potential risk factors, to verify the safety of new licensed vaccine through post-marketing studies and to be reactive in case of suspected adverse events reported by the media, as discussed in the 24 articles presented in this review,<sup>94–116,137</sup> because the trust building process is very complex and long, and it could be undermined in an instant.<sup>138</sup> In fact, in the case of a health crisis (i.e., new outbreak, alleged AEFIs), public opinion is formed within the first 24 h; that is why health institutions need to provide timely, transparent, true, coherent and credible information,<sup>138,139</sup> particularly for vaccinations that are administered routinely in healthy people to prevent disease.

In Valencia, Spain, the IIS was set up in 2002, and in 2005, recording of AEFIs was allowed through the IIS. From the analysis of the period 2005–2011, including information about vaccine safety and reported AEFIs according to patient characteristics (age and sex) and type of vaccine administered, it was possible to identify an increase in local reported reactions due to the switch from DTaP to Tdap.<sup>94</sup> Another example of IIS connected to AEFI surveillance system is the Alberta IIS, where AEFIs related to HPV vaccination were explored.<sup>108</sup> Among 195,270 women who received the vaccine, only 192

reported AEFIs. They were also able to know the type of AEFI reported, how many days after the immunization, associated dose, if hospitalization was required and the outcome. Among the AEFIs found, in the majority of cases, they happened after the first dose ( $n = 117$ ). The most common AEFIs reported were 90 allergic reactions, 32 rash, 34 unusual reactions and 23 swelling or pain. Out of these, only five were hospitalized, four within 42 d after vaccination and one after 110 d. All the hospitalized women were alive, the ICD-10 diagnostic codes were available for three of them: one was “other physical therapy”, one was “chest pain unspecified” and the last one was “phlebitis and thrombophlebitis of other deep vessels of lower extremities”. Dey et al. used the Australian IIS – where AEFIs are routinely reported – to detect an early-onset signal of adverse reactions.<sup>101</sup> After a punctual evaluation of the AEFIs recorded, the increased rate was clearly imputable to one specific vaccine manufacturer when compared to the others. It is an important example of timely and sensitive methods to assess adverse events associated with immunization. It was also possible because of traceability of vaccine lots, highlighting the relevance of accuracy in reported batches.

### **Social mobilization to promote vaccine programs**

Previous studies evaluated the association between maintaining immunization records and the increase of vaccine coverage rates.<sup>140</sup> McElligott and Darden conducted a national validated survey aimed to assess availability of vaccination records among households with children between 19 and 35 months of age and assess if updating the vaccination database may increase the vaccination rate.<sup>141</sup> After stratification for numerous variables (ethnicity, parent education level, number of children at home, poverty status), they found a statistically significant relationship between having a vaccination record and immunization rate, for all variables. Moreover, having vaccination records increased the odds of being updated compared to not having vaccine records by 62%. These increasing vaccination rates among the group with vaccination records highlight the importance for parents to have a record, in order to have more control of children’s health, and for HCW to double check the vaccination status at every visit. One of the new challenges for IIS is migration, which can reduce a person’s own data availability; however, two papers have shown potential solution to this aspect.<sup>117,118</sup> Wilson et al. proposed mobile phone software as a possible solution.<sup>118</sup> In fact, apps connected to IIS might consolidate data from multiple sources and, after an internal validation, it can provide a platform where people are engaged with their own vaccine information. Moreover, it can be consulted in all possible settings, increasing people’s awareness and accuracy in vaccine rate estimation. Control vaccination rates are essential to modulate public health efforts and to increase people’s awareness on vaccines that may dominate VH. An example of advocacy is the pro-vaccination campaign launched on Instagram by an Italian mother who was worried about the decreasing vaccination rate.<sup>142</sup> This “case-report” approach, also used by anti-vaccine movements, was aimed to motivate reluctant parents to vaccinate their child. This proactive movement overflow in a very short time into all other

social networks is the needed evidence of a bottom-up approach.<sup>142</sup> Actually, Brunson in her anthropological study evaluated the role played by social networks (in person and sources of information) on parents’ vaccination decisions. This study has shown that both people and social media are essential to formulate vaccination decisions. In particular, among those who decide to get their child vaccinated, the people network was supportive of a conformal recommendation, instead of un-(under)immunized parents. Conversely, the highest percentage of network people recommended non-conformity was found in un-(under)immunized parents. HCWs were considered for both groups, the second important network member after their own partner; other network members included were friends, family members, coworkers, midwives and university professors. This study suggests that social networks largely influence vaccination decisions in both groups. Furthermore, it is essential to develop vaccine promotion programs engaging the whole community, instead of just parents, because of the high importance of parents’ network members.<sup>143</sup> In general terms, positive social mobilization in vaccine programs (even through implementation of IIS) might be crucial to reduce VH, increase “confidence” (3Cs model) and consequently increase vaccination rates.

### **Geographical distribution, challenges and barriers and clusters of vaccine hesitant**

Increasing evidence shows a relationship between geographical clustering of unvaccinated and localization of VPD outbreaks. In this review, we synthesized results from 13 studies.<sup>119–131</sup> Eccles et al., using a geographical visualization method and IIS, assessed how geographical distribution of those who refuse vaccine had changed during a certain period and over time, identifying specific areas of non-vaccinated.<sup>125</sup> This geographical distribution has high public health impact, both to identify areas with health systems or ethnic-religious barriers and to identify areas with sanitary issues. In fact, known reasons for un-immunization are health-care access barriers, such as the time needed to reach the health care unit or the presence of public transportation or accessible parking; ethnic-religious barriers and socioeconomic barriers such as poverty, immigrant status, high residential density, material deprivation and high violent crime rates, as Charland and colleagues have shown.<sup>119</sup> These factors are part of “convenience” of the 3C model. IIS is a good instrument to assess vaccine coverage and vulnerability of unvaccinated people; moreover, it is a powerful instrument for public health investigations. Thompson et al. employed this instrument to assess vaccination rates and geographical distribution after the outbreak of measles in DisneyLand, Florida;<sup>128</sup> while Teng and colleagues, after the worst cholera outbreak in Haiti, were able to monitor the massive campaign and through the global positioning system mapped the vaccination post locations and the geographical distribution of community coverage.<sup>127</sup> IIS and geographical data are also decisive to assess the equity access of vulnerable populations such as the Australian Aboriginal. A study evaluating the Indigenous vaccination rate in relation to accessibility or remoteness, (graded in five categories, according to Accessibility/Remoteness Index of

Australia) found that pneumococcal conjugate vaccine immunization coverage ranged between 0.06% in very remote areas and 28.8% in accessible districts.<sup>121</sup> However, the coverage was suboptimal even in highly accessible areas with a range between 2.7% and 92.2% among Indigenous children aged 3 months. Using the same index, it was also possible to assess the timeliness of the first three doses of diphtheria, tetanus, pertussis (DTP), *Haemophilus influenzae* type b and MMR vaccines among Aboriginal children (aged at least 36 months in accordance with Australian vaccine schedules) even in relation to remoteness.<sup>122</sup> Timeliness and completeness of vaccination data and Indigenous status were assessed by Australian IIS. Delayed vaccine delivery was 3–5 times higher among Indigenous children compared to non-Indigenous children. In particular, for the last DTP dose, the delay was higher among Indigenous children living in remote areas compared to Indigenous children residing in accessible areas.

Trogdon and Ahn, using data from IIS, found a geographical cluster of vaccination coverage in North Carolina. The geographical areas, based on ZIP code, tended to have vaccination coverage similar to their neighbors.<sup>130,144</sup> Geolocalization could also be useful to drive allocation of scarce governmental resources in initiatives where it is needed most.<sup>120</sup> Indeed, during an epidemic outbreak, vaccine campaign not only needs to first target people with a higher risk (for complications or for epidemiological reasons) but it also needs to take into account the geographical distribution of the outbreak. Keeling and White, with their mathematical model demonstrated the importance to first vaccinate the geographical areas with the higher transmission rates of the previous years,<sup>145</sup> because the spatial heterogeneity could reflect the potential sociodemographic heterogeneity.

## Discussion

Because of the complexity and the dynamism of vaccine skepticism, it is important for public health institutions to invest as much as possible in studies evaluating vaccine safety and communication strategies. In fact, it is essential to advocate to people about relevance, safety and vaccine effectiveness,<sup>146</sup> to offer them a dedicated website to easily find precise scientific information in plain language and, finally, to teach them how to elaborate search strategies and how to flush out fake websites.

Development of IIS could generate beneficial effects for several aspects of immunization policy, such as estimation of vaccination coverage, vaccine efficacy and safety. Particularly, in this review, we presented the principal potential functions of IIS useful to reduce VH in an empowered way for both health-care workers and general population. Through the 3C model of VH, we discussed the beneficial aspects of IISs. We focalized our attention on (a) automatic reminder/recall, (b) characteristics of vaccines refusers and vaccines recipients, (c) interoperability, missed opportunities and decision support system, (d) IIS as an instrument to vaccine program performance, (e) possibility to record AEFI, (f) social mobilization to promote vaccine programs, (g) geographical distribution and cluster of vaccine hesitants.

In relation to automatic reminder/recall, IIS feedback to vaccine providers might reduce vaccine delay and missed vaccination opportunities. IIS might also be an instrument to assess vaccine providers' performance and to assign incentives. Actually, with a reminder/recall automatic system, IIS can increase people compliance to vaccination and vaccine knowledge whether the reminder is also associated with educational information. Whilst, if the feedback/reminder, based on vaccine coverage, is sent to the health care workers, it could increase the communication opportunities on vaccines and reduce the missed opportunities. Furthermore, IIS could be useful to combine several types of activities (financial incentives, share strategy and policy)<sup>83</sup> and provide basic information on vaccine counseling during the feedback, in order to be able to experience both health prevention and promotion. IIS could be a very useful instrument for HCW and for public health program managers to identify characteristics of vaccines refusers and vaccines recipients. Indeed, IIS is strategic to assess, monitor and address the determinants of hesitancy and to sustain efforts to enhance vaccination confidence and uptake. Further, the reduction of missed opportunities, thanks to IIS, may, in addition, increase the frequency of recommendations from HCW to patients. This can reinforce the perception of the relevance of vaccinations among patients, resolve possible patient doubts or hesitancy about vaccines and can also transmit health information. In fact, despite 59–81% of surveyed US adults having used the internet to get health information,<sup>147,148</sup> physicians remain the highest trusted information source among patients.<sup>149</sup>

Regarding the evaluation of vaccine campaign performance, the IIS only represents an instrument to evaluate or compare different vaccine policies: how they impact vaccine coverage and cost effectiveness, and they give scientific support to policy makers, independently of potential coercion.<sup>146</sup> IIS could concretely represent a valid instrument to increase “confidence”, and especially trust, in both HCW and decision makers.

The possibility to record AEFIs in IIS might help to generate spot signals in the safety surveillance system. It would also help to identify a specific questionable lot and consequently to retrospectively identify who received the vaccine and from which specific lot. Additionally, it allows activation of the specific action required. In other words, IIS represents an excellent instrument to record, and to make available, more information on the event compared to the standard form for AEFI system.

Post-licensure surveillance of AEFIs is an integral part of immunization programs. IIS provides useful information, such as trends and signals that can be detected. In particular, IIS with AEFI records allowed easy and quick evaluation of potential adverse events and, subsequently, planning of a timely, credible and complete communication campaign, avoiding the spread of misleading information.<sup>150</sup> An example of this could be the so-called Fluad case during the 2014/2015 influenza vaccination campaign in Italy.<sup>151</sup> Indeed, after an erroneous report of four suspected deaths caused by administration of influenza vaccine, the influenza vaccine uptake dramatically dropped.<sup>150</sup> Certainly, the concept of “balanced information” in this case is essential. However, the availability of timely and accurate data may contribute in preventing misinformation.<sup>152</sup> It is particularly true

considering that low trust in institution and fear of vaccine safety are the most frequent reasons of VH. In this sense, the possibility to record AEFIs could help in countering VH. In other words, IISs may easily evaluate vaccines safety also through individuals data linkage with other electronic systems that are part of the e-Health initiatives which are developing quickly and they will be very useful to general population, vaccine providers and health authorities. Clearly, IIS with AEFIs, and consequently its rapid consultation, may increase people's "confidence", improving trust particularly in vaccine safety. Moreover, it is noteworthy that continuous recommendations from physicians, updated education on vaccines for HCWs, traceability of immunizations records and dissemination of scientific evidence in plain language are milestones in facing vaccine delay or hesitancy. All of these are potential IIS functions that can improve the quality of the service, increasing "convenience" and "confidence". The use of IIS at full operating speeds might represent an efficient tool to bridge the gap in vaccine coverage rates. Lastly, the possibility to geolocalize in detail the districts with low vaccination rates might underline the presence of potential issues, can allow to know more in depth the characteristics of the people in these areas and may support more tailored interventions to face specific needs.

Lastly, IIS can also reduce entry errors. Indeed, because IIS is an electronic system, the data entry could be carried out electronically, for instance vaccine bench codes, bar codes or drop-down menus could be used instead of manual data entry. Such innovative immunization surveillance system may be extremely useful also in rural area and in developing countries where computing infrastructures are very limited.<sup>153</sup> Inversely, mobile phones are very promising, because they are cheaper, easily used by HCW, with low power consumption and ubiquitous. Furthermore, mobile app can also be useful for cross-border travelers who have to show the International Certificate of Vaccination, for instance yellow fever, when arriving in countries where this is mandatory. Digital immunization passports could be beneficial for both public health purpose and users. In fact, if information could be stored centrally, more data could be recorded and the digital identification could be less prone to forgery.<sup>154</sup> Blockchain is a real-time digital technology that allows any user to figure out who owns what, where and when within a hypothetical supply chain.<sup>155</sup> This technology would be very helpful in those situations where vaccine supply chain should be warranted and a supply chain disruption may affect seriously vaccine uptake, which is the case of vaccine delivery in developing countries. In addition, the blockchain technology may ensure secure data access and patient privacy when it comes to distribute information coming from IIS.

Nevertheless, IIS is not without potential limitations. Researchers during IIS studies often face other obstacles, such as data sharing and confidentiality, or the overestimation of the denominator used to calculate the coverage rate.<sup>156</sup> The number of people who moved to another state or region but remain active in the IIS could explain this. Indeed, the completeness and accuracy of the denominator is one of the limits of IIS. It could be due principally to the absence of a unique identifier number assigned to the citizens or the absence of multiple

sources for denominator data, which are characteristics considered important for IIS in order to fully support the immunization programs. Several possibilities can be offered to address this problem. For instance, reminder/recall systems can help to identify the cross-border child, the system could allow their citizens to update their own information<sup>108</sup> or an IIS interconnected with civil registries could reduce this bias.<sup>157</sup> Timeliness is another aspect that should be taken into account. Indeed, in order to reduce missing data or data entry error, the time between vaccination administration and data record should be reduced. Finally, the adoption of electronic devices requires a huge investment both in terms of time and financial resources.<sup>158</sup> Another potential limit of the IIS is the upgrade of the functionalities such as the cross-talk between different registries. Registries may differ in terms of aims (e.g., cancer registry, civil registry) and, in the case of subnational IIS, different counties or districts could have different software.<sup>159</sup> Nevertheless, the potential benefits in terms of vaccine program quality, high vaccine rates, decrease of social disparities and VH, are invaluable. Indeed, IIS also represents an instrument to evaluate or compare different vaccine policies, how they can affect vaccine coverage and cost effectiveness and give scientific support to policy makers. IIS could concretely represent a valid instrument to increase "confidence" and "convenience", especially trust in both health-care workers and decision makers and to reduce "complacency". Nowadays, VH is one of the most important issues in public health; therefore, it is mandatory for public health workers to find new strategies able to address this problem. Currently, the international public health institutions are focusing on communication, but this could not be enough. Developing and improving IISs could represent one useful tool to improve communication, confidence and convenience on immunization programs. VH is a complex phenomenon where complacency, confidence and convenience are the three main decision factors. The results of this review show that IISs are important instruments to counter VH; nevertheless, there are not enough trials aimed to evaluate the efficacy of IIS to contrast VH. Further researches should focalize on this aspect.

Lastly, the present review had some limitations. Indeed, due to the newness of this topic, there is a wide variation in the indexed terms used in PubMed and Embase to describe IIS. However, to the best of our knowledge, this is the first review analyzing the application of IIS in order to counter VH.

## Conclusion

In conclusion, some of the potential applications of IISs are get data on refusers' characteristics, such as geographic distribution; be aware of the personal immunization status, which appear much more important in the current context of migration/globalization and social mobilization; get data on potential adverse effects following immunization, increasing the vaccine's confidence and people trust.<sup>160</sup> The use of IIS is a promising tool useful for both vaccine providers and vaccine recipients as well as public health policy makers and epidemiologists.<sup>13,161</sup> It allows access to flexible analyses that cannot be done using other vaccination data sources. It is able to reduce the burden of manual paper reporting systems, to facilitate quarterly vaccine coverage reports instead of aggregate data, to increase the

accuracy of the data and to track the administered doses.<sup>162</sup> Recent systematic reviews gave an overview of the possible IIS uses in public health.<sup>163,164</sup> However, Curran and colleagues have stated that the IIS is probably used below its real potential, as shown by an exponential increase of published articles only in the last few years.<sup>156</sup>

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