Journal of Infection (2017) 74, S101—S107

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Generalized herd effects and vaccine evaluation: impact of live influenza vaccine on off-target bacterial colonisation

Michael J. Mina [a,*]

[a] *Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, 02115 USA*

Available online 23 June 2017

KEYWORDS
Vaccines;
Herd-effects;
Generalized herd-effects;
LAIV;
Influenza;
Pneumococcus;
Coinfection

Summary Interactions between pathogens and commensal microbes are major contributors to health and disease. Infectious diseases however are most often considered independent, viewed within a one-host one-pathogen paradigm and, by extension, the interventions used to treat and prevent them are measured and evaluated within this same paradigm. Vaccines, especially live vaccines, by stimulating immune responses or directly interacting with other microbes can alter the environment in which they act, with effects that span across pathogen species. Live attenuated influenza vaccines for example, while safe, increase upper respiratory tract bacterial carriage density of important human commensal pathogens like *Streptococcus pneumoniae* and *Staphylococcus aureus*. Further, by altering the ecological niche and dynamics of phylogenetically distinct microbes within the host, vaccines may unintentionally affect transmission of non-vaccine targeted pathogens. Thus, vaccine effects may span across species and across scales, from the individual to the population level. In keeping with traditional vaccine herd-effects that indirectly protect even unvaccinated individuals by reducing population prevalence of vaccine-targeted pathogens, we call these cross-species cross-scale effects "generalized herd-effects". As opposed to traditional herd-effects, "generalized" relaxes the assumption that the effect occurs at the level of the vaccine-target pathogen and "herd effect" implies, as usual, that the effects indirectly impact the population at large, including unvaccinated bystanders. Unlike traditional herd-effects that decrease population prevalence of the vaccine-target, generalized herd-effects may decrease or increase prevalence and disease by the off-target pathogen. LAIV, for example, by increasing pneumococcal density in the upper respiratory tract of vaccine recipients, especially children, may increase pneumococcal transmission and prevalence, leading to excess pneumococcal invasive disease in the population, especially among the elderly and others most susceptible to pneumococcal disease. However, these effects may also be beneficial, for example the large reductions in all-cause mortality noted following measles vaccines. Here we discuss evidence for these novel

* Corresponding author. Department of Pathology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115 USA.
E-mail address: mjmina@bwh.harvard.edu (M.J. Mina).

vaccine effects and suggest that vaccine monitoring and evaluation programs should consider generalized herd effects to appreciate the full impacts of vaccines, beneficial or detrimental, across species and scales that are inevitably hiding in plain sight, affecting human health and disease.

Introduction

Infectious diseases are most often considered independent, with most information, and by extension clinical and regulatory decision making based on a traditional one-host one-pathogen paradigm.[1] Interventions to treat and prevent infectious diseases, such as antimicrobials and vaccines therefore follow this same paradigm. Numerous examples however, as well as an infusion of research into the host microbiome demonstrate the importance of within-host interactions across multiple microbial species, pathogenic and commensal, in dictating health and disease.[1–4] Within-host cross-species interactions may be mediated indirectly, through the host immune system, for example susceptibility to *Mycobacterium tuberculosis* in the context of human immunodeficiency virus (HIV) immune depletion,[5,6] or via direct microbial interactions, for example the ability of *Staphylococcus aureus to* utilize the hyphal components of *Candida albicans* during coinfection to enhance invasion.[7] Therapeutics and other interventions that perturb microbial organization may have important unintended benefits, or potentially undesirable detrimental effects. Antibiotics that augment gut microbial cooperation, metabolism and regulation can open the door for opportunistic pathogens, with sometimes devastating results.[8,9] Indeed, antibiotic associated *Clostridium difficile* infections are now the most common health-care associated infections in the United states.[9] Alternatively, therapeutics and vaccines can harbor unexpected benefits to reduce disease from non-targeted pathogens.[10,11]

Additionally, assessment of infectious diseases, and the interventions to treat, control, and prevent them (e.g. antibiotics and vaccines) most commonly consider effects within a single spatial or temporal scale.[1] Mechanism and pathogenicity for example are understood to be at the molecular or single species level and are usually considered over the course of minutes or hours, clinical interventions are assessed at the individual level, often over days or weeks, and epidemics are most commonly viewed as population processes, explored over weeks, months or years. Rarely do these spatiotemporal scales overlap in the medical infectious disease literature, with a notable exception for vaccine herd-immunity.[12] Even less frequently do considerations of multi-species interactions merge with multi-scale spatiotemporal thinking. Consequently, policies, procedures and regulatory bodies that influence how and when antimicrobials and vaccines are utilized remain focused on a robust but relatively limited knowledge set that exists primarily within the one-host one-pathogen paradigm.[13,14] Without looking beyond this, important benefits of these interventions might be missed[10,15–17] (and see our article 'Measles, immune suppression and vaccination: direct and indirect nonspecific vaccine benefits' in this same issue) and potential adversities could go undetected.[14,18–21]

We have explored these issues using a new twist on a well characterized interaction between influenza viruses and the bacteria *Streptococcus pneumoniae*,[22] a commensal pathogen and common colonizer of the upper respiratory tract.[23]

Proof of principle: cross-species vaccine effects

Influenza vaccines and bacterial respiratory pathogens

To achieve licensure, influenza vaccines, like all vaccines, are evaluated first and foremost for safety, and secondarily, for efficacy to prevent infection by the target pathogen. Vaccine assessment does not usually consider effects on infections considered to be unrelated, such as viral influenza vaccine effects on bacterial infections. Additionally, vaccine monitoring focuses almost exclusively on efficacy at the scale of the vaccine recipient, though additional consideration is given to herd immunity.[24] Never however, to the best of our knowledge, has a formal vaccine safety and monitoring assessment directly addressed vaccine effects that may occur both across species from the target pathogen and across scales, to unvaccinated individuals.

As a proof of principle, we explored the effects of live attenuated influenza vaccination (LAIV) on carriage or infection by bacterial commensal pathogens.[20,22] We also explore here, conceptually, how such within-host effects of a viral vaccine might alter the population-level prevalence of respiratory bacterial pathogens. These cross-species, cross-scale effects would be outside the scope of any modern evaluation of the safety and efficacy of a viral vaccine.

We chose LAIV as a model vaccine because its target pathogen, wild-type (WT) influenza is famous for, among other traits, predisposing to severe secondary bacterial infections – the most famous example being the 1918 influenza pandemic, that killed an estimated 50 million people worldwide, largely a result of post-influenza bacterial complications.[25,26] A plethora of clinical and laboratory research has since shown that infection with the influenza virus abrogates innate and adaptive immune defenses, reduces tolerance to tissue damage, and disrupts normal immune signaling and feedback mechanisms (reviewed[22,27,28]). Collectively, these increase susceptibility to bacterial acquisition, allow relatively unrestricted bacterial replication in the upper and lower respiratory tract, and enhance susceptibility to and severity of secondary bacterial otitis media, pneumonia and invasive disease.[26,29]