Beneficial non-specific effects of live vaccines against COVID-19 and other unrelated infections

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Live attenuated vaccines could have beneficial, non-specific effects of protecting against vaccine-unrelated infections, such as BCG protecting against respiratory infection. During the COVID-19 pandemic, testing of these effects against COVID-19 was of interest to the pandemic control programme. Non-specific effects occur due to the broad effects of specific live attenuated vaccines on the host immune system, relying on heterologous lymphocyte responses and induction of trained immunity. Knowledge of non-specific effects has been developed in randomised controlled trials and observational studies with children, but examining of whether the same principles apply to adults and older adults was of interest to researchers during the pandemic. In this Personal View, we aim to define a framework for the analysis of non-specific effects of live attenuated vaccines against vaccine-unrelated infections with pandemic potential using several important concepts. First, study endpoints should prioritise severity of infection and overall patient health rather than incidence of infection only (eg, although several trials found no protection of the BCG vaccine against COVID-19 infection, it is associated with lower overall mortality than placebo). Second, revaccination of an individual with the same live attenuated vaccine could be the most effective strategy against vaccine-unrelated infections. Third, coadministration of several live attenuated vaccines might enhance beneficial non-specific effects. Fourth, the sequence of vaccine administration matters; the live attenuated vaccine should be the last vaccine administered before exposure to the pandemic infection and non-live vaccines should not be administered afterwards. Fifth, live attenuated vaccines could modify the immune response to specific COVID-19 vaccines. Finally, non-specific effects of live attenuated vaccines should always be analysed with subgroup analysis by sex of individuals receiving the vaccines.

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Introduction

Live attenuated vaccines have been linked to beneficial non-specific effects, such as reductions in mortality that are not explained by preventing the vaccine-targeted disease.[1–6] Randomised clinical trials (RCTs) have repurposed measles vaccines, the BCG vaccine against tuberculosis, and oral polio vaccine (OPV) to reduce child mortality by providing protection against vaccine-unrelated infections.[1–6] Immunological studies of BCG have shown that two main mechanisms could mediate the non-specific effects of live attenuated vaccines. First, heterologous T-cell immunity can induce responses against the non-target pathogens through molecular mimicry (eg, there is 80% similarity between SARS-CoV-2 open reading frame 7a protein epitope with the human poliovirus type 3 Sabin strain epitope).[7] Second, many live attenuated vaccines can induce long-term functional reprogramming of innate immune cells due to epigenetic and metabolic rewiring of immune cell progenitors, leading to enhanced antimicrobial function known as trained innate immunity.[8–10] Induction of trained immunity is also associated with decreased systemic inflammation,[11] and induction of tolerogenic effects could be responsible for some of the protection reported against sepsis and COVID-19.[12]

Beneficial non-specific effects that reduce infections with unrelated pathogens are precisely what could help to control infections that have the potential to become pandemics until novel specific vaccines are built, tested, and distributed. Although non-specific effects will not provide full protection from the pandemic infection, they might reduce susceptibility, limit transmission, and reduce severity.[13] These effects could slow pandemics and minimise damage to health and society, thus increasing the time in which disease-specific treatments and vaccines can be developed. Therefore, many research groups have studied potential effects of BCG against COVID-19 early in the COVID-19 pandemic.[14,15] Importantly, more than 20 RCTs were initiated; most tested BCG,[16,17] but RCTs of OPV and vaccines for measles, mumps, and rubella (MMR) were also initiated.[16]

COVID-19 vaccines were quickly developed after the COVID-19 pandemic began, so the urgency to use live attenuated vaccines against COVID-19 mostly disappeared. However, even if booster vaccines of COVID-19 provide satisfactory long-term protection, live attenuated vaccines should continue to be studied as a potential tool for future pandemics. New infections will continue to be identified in the future, and some will develop into pandemics. It might not be possible to develop vaccines for all emerging pathogenic threats at the same speed as was done with COVID-19 vaccines and it would be desirable to have some temporary vaccines that could provide at least partial protection in the beginning of a pandemic.

There are fundamental differences between testing vaccines against a specific disease and testing their potential non-specific effects. In this Personal View, we present a framework for the optimal assessment of the non-specific effects of live attenuated vaccines against COVID-19 and other vaccine-unrelated infections. We summarise important principles for non-specific effects to help define which factors might modify them, as well as how to test them in more depth.

See Online for appendix

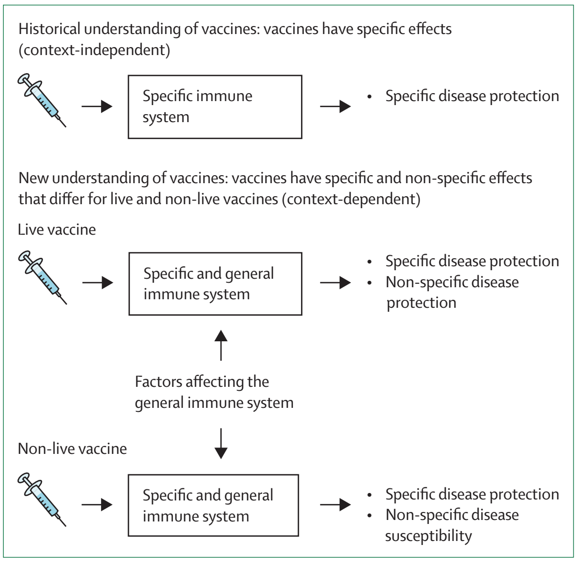

Figure: **Non-specific effects of vaccines are affected by factors affecting the general immune system**

Context-dependence of non-specific effects

It is simple to test whether a vaccine induces protective immune responses or prevents the target infection in real-life settings if vaccine efficacy can be measured. Testing a specific vaccine is thus context-independent (figure).

Non-specific effects of vaccines were discovered in RCTs and observational studies of paediatric vaccinations.[18,19] Live attenuated vaccines reduced mortality more than was explained by protection against the vaccine-targeted disease; thus, live attenuated vaccines were known to confer protection against unrelated pathogens.[5,13,20] Mechanisms that could explain this protection include trained innate immunity and heterologous T-cell immunity. Trained immunity means increased responsiveness towards unrelated pathogens generated by epigenetic reprogramming of innate immune cells.[8–10] In addition, vaccines might introduce heterologous T-cell responses that generate increased production of host defence factors, such as interferon γ in response to cytokine release by innate immune cells.[21,22] The ability of live attenuated vaccines to induce stronger non-specific effects than non-live vaccines might be because live attenuated vaccines mimic an infection in a more natural way that a non-live vaccine. Many live attenuated vaccines are also their own adjuvants that more broadly stimulate innate and adaptive immune cells, whereas many currently used adjuvants (eg, alum) have very restricted activity on stimulating B-cell responses. Some adjuvanted non-live vaccines, such as the influenza vaccine or the varicella-zoster vaccine, also display heterologous effects.[23,24]

As non-specific effects occur due to modulations of the immune system, their magnitude can be changed by other interventions or contextual factors that affect the immune system. Non-specific effects are context-dependent (figure). For example, in RCTs the relative mortality of the live attenuated vaccines and control groups can change completely due to other interventions (appendix pp 2–3). Epidemiological studies gradually identified interactions that changed the overall non-specific effects of measles vaccines in different contexts (appendix pp 5, 6). In the past 2 years, an understanding has emerged of some important principles of non-specific effects and how other interventions or contextual factors might modify them.[1]

Vaccine studies typically focus on outcomes, such as antibody titres or clinical protection against a specific infection. By contrast, the non-specific effects of live attenuated vaccines have been shown to reduce general mortality and protect against infections other than those caused by the vaccine pathogen. These non-specific effects are not fully protective against vaccine-unrelated infections and might depend on other factors that affect health. Therefore, studies of non-specific effects that evaluate them in the typical context-independent way might incorrectly dismiss an effect. However, non-specific effects can provide important benefits through partial protection against infections for which effective vaccines and treatments might not be available. Thus, it is essential that studies of live attenuated vaccines against COVID-19 assess their results in relation to existing knowledge about the context-dependence of outcomes.

Key principles of non-specific effects and implications for ongoing studies

Live attenuated vaccines have beneficial non-specific effects

Beneficial non-specific effects have been seen in humans for BCG, measles vaccines, MMR, OPV, and smallpox vaccines (appendix pp 2–3).[18] By contrast, six non-live vaccines, although protecting against the target infection, are associated with increased mortality in female individuals[1] (possibly linked to induction of innate immune tolerance).[10] The duration of non-specific effects is poorly defined as they can change when another vaccine is administered (eg, the birth dose of BCG only has beneficial non-specific effects until diphtheria-tetanus-pertussis vaccine [DTP] is administered at around age 6 weeks). Measles vaccines could have beneficial non-specific effects for up to 2 years if non-live vaccines are not administered afterwards.[2,25]

BCG, OPV, and measles vaccines with beneficial non-specific effects in children are currently being assessed to establish whether they have beneficial effects against pandemic infections in adults. Studies of adults or individuals older than 65 years should analyse potential timing effects to establish a better understanding of how long non-specific effects could last and when additional doses of vaccines might be needed. Other live attenuated vaccines could also be tested for beneficial non-specific effects, such as yellow fever, rotavirus, varicella, live

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	Vaccine	Main outcome	Design	Age interval	Percentage of deaths to person-years of observation (n/N)	Morbidity or mortality RR* (95% CI)
BCG						
Algier (1935–52)[29]	Oral BCG2	Mortality	Alternation of BCG administered at birth or no BCG administered on the basis of civil registration number	1 year to 2 years	5·9% BCG2 (1721/29 310); 7·1% no BCG (1919/27 233)	0·83 (0·78–0·89)
Algier (1935–52)[29]	Oral BCG3	Mortality	Alternation of BCG administered at birth or no BCG administered on the basis of civil registration number	3 years to 4 years	1·0% BCG3 (243/25 444); 1·8% no BCG (414/23 034)	0·53 (0·45–0·62)
Guinea-Bissau (2002–06)[30]	Intradermal BCG	Mortality	Randomisation to BCG2 or no BCG2; only individuals with booster DTP at age 18 months were included	19 months to 5 years	0·4% BCG2 (5/1393); 1·0% no BCG (14/1406)	0·36 (0·13–0·99)
Measles vaccine						
Guinea-Bissau (1980–82)[31]	Measles vaccine	Mortality	Natural experiment; children with measles vaccine administered before age 9 months received MV2	9 months to 60 months	Not provided	0·41 (0·19–0·75)
Guinea-Bissau (1992–94)[32]	Measles vaccine	Mortality	RCT; DTP not given with measles vaccine; only children with DTP3 administered before age 9 months were included	9 months to 18 months	0% MV2 (0/72·1) *vs* 2·8% MV1 (2/70·3)	0 (0–3·95)
Guinea-Bissau (2003–09)[33]	Measles vaccine	Mortality	RCT; DTP not administered with measles vaccine; all participants had DTP3 administered before measles vaccine	9 months to 19 months	1·1% MV2 (8/713·9) *vs* 2·9% MV1 (39/1370·5)	0·39 (0·18–0·83)
Guinea-Bissau (2016–19)[34]	Measles vaccine	Severe morbidity (mortality and admissions to hospital)	RCT done with individuals aged 18 months; MV2 *vs* no MV2; severe morbidity at ages 18–48 months	18 months to 48 months	2·6% MV2 (18/690); 3·6% control individuals (25/690)	0·72 (0·38–1·38)
OPV						
Guinea-Bissau (2002–14)[35]	OPV	Mortality after OPV campaign *vs* mortality before OPV campaign	Natural experiment; effect of each additional dose of campaign OPV was measured	1 day to 3 years	OPV-only campaigns: effect of each additional campaign	0·86 (0·81–0·92)
Bangladesh (2004–19)[36]	OPV	Mortality after OPV campaign *vs* mortality before OPV campaign	Natural experiment; effect of each additional dose of campaign OPV was measured	1 day to 3 years	OPV-only campaigns: effect of each additional campaign	0·94 (0·87–1·02)

BCG2=second dose of BCG. BCG3=third dose of BCG. DTP=diphtheria-tetanus-pertussis vaccine. DTP3=third dose of diphtheria-tetanus-pertussis vaccine. MV1=first dose of measles vaccine. MV2=second dose of measles vaccine. OPV=oral polio vaccine. RCT=randomised clinical trial. RR=risk ratio. *Morbidity risk ratio or mortality risk ratio as indicated in the main outcome column.

Table 1: **Studies of revaccination with live attenuated vaccines against overall mortality or severe morbidity**

shingles, live influenza, and live pertussis vaccines.[26] Some observational studies suggest that the non-live vaccines against influenza and herpes zoster could have non-specific effects against COVID-19.[24,27,28] Due to possible bias and confounding in these observational studies, RCTs are needed.

Revaccination with live attenuated vaccines might enhance beneficial non-specific effects

The first dose of a live attenuated vaccine is usually protective against death from the target infection and additional doses should not further reduce mortality. However, beneficial boosting effects on overall mortality have been found for all live attenuated vaccines (ie, BCG, vaccinia vaccine, measles vaccine, MMR, and OPV; table 1).[33,37] For example, additional doses of campaign OPV in an individual reduced child mortality by 14% (8–19%) in Guinea-Bissau,[35,36] and BCG treatment for bladder cancer had better effects in individuals who had previously been vaccinated with BCG than in individuals with no previous BCG vaccination.[38]

It could be useful to test several doses of whichever live attenuated vaccine is being used to protect against COVID-19. We predict that when one dose of BCG is tested against COVID-19, it will work better among people who have previously been vaccinated with BCG than among people with no previous BCG vaccination.[33] With the potential importance of revaccinations, BCG scars should be registered in adult studies so whether a vaccine is a primary or a booster dose of BCG can be assessed.

To enhance protection against future pandemics, we might benefit from testing multidose schedules with BCG, OPV, MMR, or other live attenuated vaccines (table 2) and examining whether BCG in childhood and a current BCG has the same effect as two current doses of BCG. Similar studies should be done for MMR and OPV.

Maternal priming might enhance non-specific effects of subsequent BCG and measles vaccinations in offspring

The benefits of BCG or measles vaccines in infancy are increased if the mother has a BCG scar or the offspring has maternal measles antibodies at the time of measles vaccination.[33,39,40,41] Therefore, maternal priming has a

	Current study design testing live attenuated vaccines against COVID-19	Strategies for future pandemic control
Live attenuated vaccines have beneficial non-specific effects	RCTs with BCG, MMR, and OPV	Other live attenuated vaccines should be tested; a larger group of live attenuated vaccines might be needed for future pandemics
Revaccination of an individual with live attenuated vaccines enhances the beneficial non-specific effects	Most RCTs test one dose of live attenuated vaccine; RCTs of BCG could be revaccination trials because some individuals received BCG in childhood	Revaccinations are likely to be most effective for all live attenuated vaccines; eg, two doses of OPV administered in the same individual 1 month apart were used in OPV campaigns with strong effects on child survival; the most effective intervals between doses should be established in future RCTs
Maternal (and paternal) priming enhances the beneficial non-specific effects of live attenuated vaccines in offspring	COVID-19 is not severe for infants, so no current testing in this population	If the pandemic disease becomes severe for infants, test whether women of fertile age and their offspring could be given the same live attenuated vaccines (eg, BCG, OPV, and measles vaccines)
Coadministration of several live attenuated vaccines might enhance beneficial non-specific effects	Only single live attenuated vaccines have been tested against COVID-19	Coadministration of two or more live attenuated vaccines might improve efficacy, but more data are needed
Sequence of administration matters (the last vaccine administered has the strongest non-specific effects)	Current testing of live attenuated vaccines does not consider sequence of administration in relation to COVID-19 vaccines or other non-live vaccines administered during follow-up	Should probably administer live attenuated vaccines last if non-live vaccines are required (eg, influenza vaccine); assessment of live attenuated vaccines for pandemic control should continue until another type of vaccine is administered
Sequence of administration matters (coadministration of a non-live vaccine and a live attenuated vaccine is better than administering a non-live vaccine after a live attenuated vaccine)	Current testing of live attenuated vaccines does not consider coadministration with COVID-19 vaccines or other non-live vaccines	Should probably coadminister live attenuated vaccine and non-live vaccine if it is not possible to administer the live attenuated vaccine shortly after the non-live vaccine; however, RCTs are needed to test whether live attenuated vaccines should be administered before, with, or after necessary non-live vaccines
Live attenuated vaccines could modify the immue response to other vaccines	BCG might enhance the response to COVID-19 and influenza vaccines	If possible, the effects of live attenuated vaccines on responses to vaccines administered during follow-up should be tested; live attenuated vaccines might enhance the response to pandemic vaccines
Sex is likely to modify the non-specific effects of live attenuated vaccines	Although analyses usually adjust for sex, separate effect estimates are rarely given for women and men	Non-specific effects of live attenuated vaccines against pandemic infection might differ by sex; sex-specific effect estimates should always be reported
Non-specific effects have been most effective against respiratory infections and sepsis	Apart from protection against COVID-19, other effects of live attenuated vaccines among adults and older adults have rarely been reported	The effect for different types of infections should be assessed; effects might be most useful if the pandemic disease is respiratory or causes sepsis
Non-specific effects could have stronger effects on severity than on incidence of infection	Ongoing RCTs primarily test incidence of infection; both incidence and severity should be evaluated	Severity of an infection (eg, hospitalisations or death), rather than incidence, is likely to be the most accurate outcome to assess efficacy of vaccines for pandemic infections

DTP=diphtheria-tetanus-pertussis vaccine. MMR=measles, mumps, and rubella vaccine. OPV=oral polio vaccine. RCT=randomised clinical trial.

Table 2: **Important principles of non-specific effects of live attenuated vaccines and their possible implications for future pandemic control**

boosting effect for the offspring. In Denmark, BCG vaccine administered at birth had no beneficial effect if the mother had not been BCG vaccinated, whereas BCG administered at birth was associated with 35% (range 6–55) fewer infectious-disease hospital admissions at ages 0–14 months if the mother was BCG vaccinated.[42] Paternal priming could also enhance non-specific effects of BCG vaccination of the offspring.[43] Therefore, if infants are severely affected by new infections, maternal priming with BCG or measles vaccine and subsequent early offspring vaccination with these live attenuated vaccines could increase the resistance of children to a new pandemic infection.

Coadministration of live attenuated vaccines might enhance beneficial non-specific effects

Two RCTs have tested coadministration of live attenuated vaccines. One tested BCG and OPV versus BCG only;[3] BCG and OPV was associated with a 32% (range 0–55) reduction in infant mortality until individuals received campaign OPV. In the other, coadministration of OPV and measles vaccine reduced diarrhoea morbidity compared with receiving only measles vaccine.[44,45] Different live attenuated vaccines probably affect the immune system in different ways.

Although data are scarce, it could be important to examine whether coadministration of multiple live attenuated vaccines will enhance protection against infections compared with just one live attenuated vaccine.

Sequence of vaccinations

Epidemiological studies of DTP, inactivated polio vaccine, and hepatitis B vaccine have shown that non-live vaccines administered after live attenuated vaccines reduce the beneficial non-specific effects of the live attenuated vaccines.[1] For example, DTP administered after measles vaccine is associated with double the mortality than measles vaccine administered after DTP (appendix pp 2–3).[1,46–48] Since the last vaccine in a sequence of vaccinations has the strongest non-specific effects, administering a live vaccine last is associated with the highest child survival.[46,49] Most vaccines for older adults are non-live, such as the influenza vaccine, pneumococcal conjugate vaccine, or the shingles vaccine. To optimise the use of live attenuated vaccines against pandemic threats, they should be administered after non-live vaccines recommended in this age group (eg, influenza vaccine). Furthermore, when assessing live attenuated vaccines in RCTs, for the most accurate assessment of the potential of the live attenuated vaccine for future pandemic control, follow-up for the main outcome should continue only until a non-live vaccine is administered to an individual (table 2).

Vaccine combinations

Combining the administration of live attenuated vaccines with non-live vaccines could reduce morbidity and mortality compared with only having the non-live vaccine as the most recent vaccination. This principle is shown in BCG coadministered with DTP, which is associated with 40–50% lower child mortality than the WHO-recommended sequence of DTP administered after BCG (appendix p 7).

In future pandemics, whether coadministration of non-live vaccines and BCG (or another live attenuated vaccine) provides stronger non-specific effects for overall mortality than administering the live attenuated vaccine before the non-live vaccines should be assessed.

Live attenuated vaccines might modify the response to other vaccines

Live attenuated vaccines might enhance the immunological response to unrelated vaccines administered concurrently, shortly after, or shortly before them (eg, BCG enhanced responses to concurrent hepatitis B vaccine and OPV[50] and previous BCG increased the functional antibody response to influenza vaccination).[51] By contrast, concurrent OPV and BCG versus BCG only was associated with fewer positive purified protein derivative tests[52] and reduced in-vitro cytokine responses to purified protein derivative stimulation.[53]

For vaccines with short-lived immune responses or for individuals with immunosenescence, coadministration with a live attenuated vaccine might possibly enhance the duration of infection protection. For example, if BCG enhances the immune response to COVID-19 vaccines as it does for the influenza vaccine,[51] the need for booster doses could be reduced. In RCTs testing BCG against COVID-19, BCG was administered before specific COVID-19 vaccines, so the understanding of adjuvant effects of BCG could be increased. One randomised clinical trial from Mexico suggests that BCG might boost the immune response to COVID-19 vaccination[54] and that individuals infected with SARS-CoV-2 had better anti-COVID-19 responses when vaccinated with BCG than individuals not administered a BCG vaccination.[55]

There are also biological and environmental factors that might modify how live attenuated vaccines train the immune system.

Sex and age might influence the non-specific effects of live attenuated vaccines

Vaccination programmes usually prescribe the same vaccination policy for both sexes. However, numerous studies have shown that non-specific effects are often sex differential. For example, BCG and measles vaccines have stronger beneficial non-specific effects for female individuals, whereas non-live vaccines are associated with higher mortality in female individuals than in male individuals.[1]

A null result could conceal a beneficial effect for one sex and a negative effect for the other (eg, MMR had a protective effect against COVID-19 for men but not for women in a 2021 Swedish study).[56] The effects might be different because COVID-19 has sex-differential effects, or because the vaccines have different non-specific effects for the two sexes. Hence, both specific effects and non-specific effects by sex should be analysed with subgroup analysis and reported in studies of pandemic interventions.[25]

Biological age might also influence the non-specific effects, although it has been studied less than effects by sex. Administration of BCG, OPV, and measles vaccines at a young age increases the non-specific effects for child survival.[3,57,58] This increase might happen because the effects of parental priming are strengthened if the live attenuated vaccine is administered to offspring at a young age. However, other age-related changes might occur in the immune system and affect the immune response to live attenuated vaccines.

Type of infection prevented

All five live attenuated vaccines have the strongest effect on respiratory infections,[5,6,20,59–61] and BCG has a strong effect on sepsis.[5] There has been little research into disease-differential effects of different live attenuated vaccines. Therefore, if new infections are not primarily respiratory or septic, the effect of the use of live attenuated vaccines might be restricted. The method of measurement of non-specific effects of live attenuated vaccines is also important.

Incidence, severity, and overall health

Ongoing RCTs are testing whether live attenuated vaccines reduce the incidence of COVID-19.[62,63,64] However, the non-specific effects of live attenuated vaccines might have little effect on the risk of infection but change the severity of infection. For example, RCTs of BCG administered to newborn babies found little effect on hospital admissions for sepsis, but the case fatality was reduced by 42% (95% CI 6–65%).[16,65] One RCT

	Population; length of follow-up	Age groups	Effect on main outcome	Mortality (deaths [n]/total [N])		Mortality RR (95% CI)
				BCG	Placebo	
Greece[66]	BCG *vs* placebo at hospital discharge; 12 months	Mean age: 80 years	Increased time to first infection after discharge	10/72	14/78	0·77 (0·37–1·63)
Greece[63]	BCG *vs* placebo at hospital discharge; 6 months	≥50 years	68% (range 21–87) reduction in COVID-19 clinical and microbiological diagnoses	0/148	3/153	0 (undefined)
Netherlands[67]	BCG *vs* placebo in older adults with comorbidity; 12 months	≥60 years	No effect on COVID-19 infection	13/3058	18/3054	0·72 (0·35–1·47)
Netherlands[55]	BCG *vs* placebo in older adults; 12 months	≥60 years	No effect on respiratory tract infections, including COVID-19 infection	2/1008	3/1006	0·67 (0·11–3·97)
South Africa[64]	BCG *vs* placebo in health-care workers; 12 months	Median age: 39 years	Did not protect against COVID-19 infection or hospitalisation	0/500	4/500	0 (undefined)
Combined analysis	NA	NA	NA	NA	NA	0·61 (0·38–0·99)

NA=not available. RCT=randomised clinical trial. RR=risk ratio.

Table 3: **RCTs in different countries of BCG versus placebo against COVID-19 or severe morbidity: the effect on mortality**

assessing the effects of two doses of MMR in the same individual found no effect on risk of COVID-19 infection measured by a PCR test but found major reductions in severity of infection in MMR-vaccinated health-care workers.[62]

An emphasis on severity of infection as an outcome might have an increased chance to detect non-specific effects. However, it might be even more important to measure general health outcomes like all-cause hospitalisations and death than to measure incidence or severity of infection as live attenuated vaccines might have non-specific effects that affect infections other than the specific pandemic infection (table 3). For example, several RCTs among health-care workers or older adults have measured the effect of BCG versus placebo for respiratory infections or COVID-19 infections. The effect on COVID-19 infection has mostly been disappointing, but BCG apparently reduces all-cause mortality (table 3).

Discussion and conclusions

As results of RCTs of live attenuated vaccines against COVID-19 are published in the future, there will be unique opportunities to define the contexts in which non-specific effects are useful and how they are affected by context-dependent factors. It took 35 years to develop the concept of non-specific effects and the important principles for paediatric vaccines.[1,18] The complexity of beneficial non-specific effects of live attenuated vaccines has been comprehensively shown as RCTs of BCG and measles vaccines have reported beneficial effects on non-tuberculosis or non-measles mortality. However, subsequent RCTs did not corroborate these findings.[39,68] The factors that explain these opposite effects are possible to identify, typically because of other interventions that affect mortality in both vaccinated children and children who are not vaccinated (appendix pp 2–3, 7).

The first trials of live attenuated vaccines against COVID-19 mostly tested BCG against SARS-CoV-2, and reasons other than immunosenescence might explain why these RCTs were non-conclusive or showed null-effects. BCG might influence severity rather than incidence of infection.[13] BCG might also need a booster response, so an effect might not be seen in populations in which few people have previously been administered with BCG. Furthermore, different BCG strains might have different non-specific effects.[68] Non-live COVID-19, influenza, or pneumococcal vaccines might interact with BCG if administered after BCG, so no beneficial effect of BCG is seen.

Null-effects of BCG against COVID-19 have been reported from the Netherlands and South Africa (table 3). By contrast, a Greek RCT showed protective effects of BCG in older adults.[63] The lack of effect in some RCTs could be related to a lack of previous BCG vaccination and the rapid implementation of COVID-19 vaccines. Importantly, all RCTs suggested a beneficial effect of BCG on overall survival (table 3).

Observational studies have supported the idea that revaccinations could be important. In the United Arab Emirates, BCG revaccination in the same individual had a strong protective effect against COVID-19.[69] In Türkiye, severity of COVID-19 infection was related to number of BCG scars.[70] One clinical study of patients with bladder cancer in Chile reported that numerous BCG vaccinations were associated with reduced risk of severe COVID-19,[71] and patients with bladder cancer in Iran who had received BCG therapy within the last year reported less frequent and milder COVID-19 infection than those who had not received BCG therapy within the last year.[72] The same effects are seen for other live attenuated vaccines; risk or severity of COVID-19 infection was reduced by MMR revaccination.[62,73–75] Furthermore, OPV revaccination of adults has been reported to have beneficial effects against COVID-19 infection in Russia.[76]

Knowledge of conditions that enhance or reduce beneficial non-specific effects of live attenuated vaccines should be obtained. The important principles are that: study design should prioritise severity of infection and overall health rather than incidence of infection; revaccination might be the most effective strategy against vaccine-unrelated infections; coadministration of several live attenuated vaccines might enhance the overall beneficial non-specific effects; live attenuated vaccines should be the last vaccine administered during the observation period; live attenuated vaccines might modify the response to specific COVID-19 vaccines; and results of the use of live attenuated vaccines should always be reported by sex (table 2).

Although the current focus of live attenuated vaccine research is the COVID-19 pandemic, the non-specific effects of live attenuated vaccines could be used for other important infections like influenza in older adults or malaria in Africa.[20,77] Studies of whether live attenuated vaccines reduce incidence or severity of influenza and associated mortality would be particularly important for future pandemic preparedness. Use of live attenuated vaccines against common infections would increase the knowledge of how much control can be obtained with the non-specific effects of different live attenuated vaccines.

Emphasising non-specific effects in disease control implies that research should focus on what produces a strong resilient immune system rather than focusing on vaccines against specific infections. From this perspective, health is defined as a well trained immune system and not as the absence of all infections. Studies of non-specific effects have shown that presence of BCG scars, compared with no BCG scars, among infants vaccinated with BCG is associated with a 40% reduction in child mortality.[78] Similarly, smallpox vaccination scars were associated with a 40–46% reduction in overall adult mortality, and an increased number of vaccinia scars led to strong beneficial effects.[37,79] By detecting these markers of a strong immune system, we can improve our knowledge of the interventions that will strengthen the general capacity of the immune system to fight pandemic infections.

Having multiple lockdowns during several years while waiting for effective and safe specific vaccines to be developed should not be the only strategy to fight the next pandemic. Increased pandemic preparedness requires that we systematically explore the potential beneficial non-specific effects of live attenuated vaccines, establish how they strengthen the general capacity of the immune system, and define the contexts in which they are most effective.

Contributors
All authors developed the idea and wrote the paper.

Declaration of interests
We declare no competing interests.

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