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Cost-effectiveness of zinc interventions in China: A cohort-based Markov model

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Abstract

Zinc acts as an important cofactor in the body and is essential for normal functions. Several zinc interventions have been implemented worldwide to improve the public's zinc status, but limited studies have assessed their cost-effectiveness. To help inform decision-making on zinc interventions to maximize benefits within a fixed budget, we took China as an example and evaluated the cost-effectiveness of three interventions, that is, supplementation, food fortification, and biofortification. As an essential group at high risk of zinc deficiency, children aged 5-14 years, who account for 10% of the Chinese population, were selected as the target group in this study. We constructed a decision-analytic Markov model to determine the cost-effectiveness of interventions in China under different scenarios. In our model, biofortification through conventional breeding was shown to be the most cost-effective approach in most scenarios. Compared with other interventions, zinc supplementation gained fewer quality-adjusted life years at a higher net cost, suggesting that this common approach may not be optimal for largescale, long-term implementation at the national level. While the robustness of the results was further confirmed by the sensitivity analysis, more research is needed to assess the cost-effectiveness of addressing zinc deficiency with other

Abbreviations: CDC, Center for Disease Control; CEA, cost-effectiveness analysis; CI, confidence interval; DALYs, disability-adjusted life years; EAR, Estimated Average Requirement; GDP, gross domestic production; GM, genetically modified; ICER, incremental cost-effectiveness ratio; IDA, iron deficiency anemia; LMICs, low- and middle-income countries; QALYs, quality-adjusted life years; RCT, Randomized Controlled Trial; RDA, recommended dietary allowance; RfD, reference dose; RR, relative risk; SE, standard error; WTP, willingness-to-pay.

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interventions. Further clinical trials are also expected to evaluate the effectiveness of zinc interventions in reducing pneumonia cases [EconLit Citations: I18, Q16, Q18].

KEYWORDS

biofortification, China, cost-effectiveness, economic evaluation, food fortification, zinc deficiency

1 | INTRODUCTION

Zinc is a vital trace element that serves multiple functions within the body. It acts as a component for numerous enzymes, contributing to essential metabolic pathways involved in structural, catalytic, and biochemical processes. Globally, zinc deficiency has been regarded as a prevalent public health issue, especially in many low- and middle-income countries (LMICs) (Caulfield & Black, 2004). It results in various adverse health effects, including stunted growth and increased risk of infections, particularly diarrhea and pneumonia in children, and several chronic diseases in adults (Deshpande et al., 2013). Zinc deficiency contributes to the mortality of approximately 800,000 children each year (Hambidge & Krebs, 2007). China has an exceptionally high prevalence rate of zinc deficiency, especially among younger generations. According to the Center for Disease Control in China (2020), the average daily zinc intake of the total population was 10.3 mg/day, which is about 18% below the recommended level. Among children and adolescents, the prevalence of zinc deficiency was reported to be even higher than the national average (China, 2020). A recent meta-analysis conducted in China shows that 27% of children and adolescents aged <14 years have low serum zinc levels (Cai-Jin et al., 2021), with 37.6% of adolescents aged 11-17 years having a daily zinc intake below the Estimated Average Requirement (Wang et al., 2017). In China, children in remote and impoverished regions, especially in central and western provinces, are particularly at risk due to local dietary habits, and limited accessibility and affordability of healthy foods (Zhang et al., 2018). According to WHO standards, appropriate interventions are needed to alleviate the burden of zinc deficiency when the prevalence of inadequate zinc intake exceeds 20%. Conversely, the prevalence of zinc overconsumption has also become a growing concern in recent years due to its potential toxicity risks and its close association with zinc supplementation (Willoughby & Bowen, 2014). To ensure the optimization of health outcomes, it is essential to strike a balance in zinc intake and carefully consider public zinc intervention practices.

In China, nutrition policies have been implemented nationwide since the middle of the 20th century. Various interventions, such as the distribution of supplements to vulnerable populations, large-scale food fortification, biofortification, and dietary diversification, have been implemented through nutrition education, school lunch programs, and other initiatives. A summary of the Chinese public health policies to increase micronutrient intake since the 1990s is provided in Supporting Information Appendix A. Recent health policies covering multiple types of interventions, such as food fortification, biofortification, and dietary diversification, implied a shift of policy direction from medical care support to nutrition improvement. While these policies conjointly support efforts to increase nutritional status and alleviate stunting and malnutrition in the previous decades, China is still confronted with limited resources and financial constraints, calling for priority setting of interventions.

There is clear evidence that investing in micronutrient interventions can effectively reduce morbidities and mortalities induced by zinc deficiency among the population. For instance, evidence on preventative zinc supplementation shows its potential to reduce pneumonia morbidity by 19% (Yakoob et al., 2011). Randomized Controlled Trials (RCTs) also demonstrated that zinc food fortification and biofortification could lower the incidence of pneumonia, vomiting, and diarrhea (Bahl et al., 2002; Sazawal et al., 2018).

In terms of economic assessment, dietary diversification is typically considered to be the most effective strategy to address zinc deficiency and generate health benefits (Muthayya et al., 2013), but the affordability for

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low-income residents and the accessibility of nutritious food in remote areas are vital constraints for promoting this intervention in rural areas. According to Ma et al. (2008), dietary diversity education in China was associated with the highest intervention cost per capita, I\$1148 (international dollars), which is 1,148,000 times higher than biofortification (I\$0.01) and food fortification (I\$0.01), and 229,600 times higher than zinc supplementation (I\$0.05). Furthermore, the accessibility of diversified diets is also limited by incomplete market development (Chege et al., 2015; Headey, 2019; Matita et al., 2021). Huang and Tian (2019) indicated that food market accessibility would drastically impact the dietary patterns in rural China, especially for residents that are not engaged in agriculture production. Meanwhile, the distribution of supplements, although commonly used for preventing micronutrient deficiency, requires capital investment and public medical education costs, which significantly burden local health system spending (Silva & Nabavi, 2019). In recent decades, several relatively affordable crops and condiments (such as grains, potatoes, oil, salt, and soy sauce) have been put forward as ideal carriers of micronutrients to improve public health cost-effectively through food fortification or biofortification, providing abundant solutions for alleviating zinc deficiencies in underdeveloped areas. Numerous studies around the world have shown that zinc supplementation, food fortification, and biofortification are highly cost-effective (Fink & Heitner, 2014; Horton, 2006; Ma et al., 2008; Mejía et al., 2015; Stein et al., 2007; Wang et al., 2016).

Cost-effectiveness analysis (CEA) has been widely implemented in project feasibility evaluations. Previous economic evaluations have articulated the cost-effectiveness of health interventions for zinc deficiency with both ex ante and ex post analysis. Findings from cost-effectiveness studies of zinc interventions (including zinc supplementation, food fortification, and biofortification) in LMICs are presented in Supporting Information Appendix B. In general, biofortification displays a low cost per disability-adjusted life years saved, suggesting its long-term cost-effectiveness.

However, most of these evaluations focus only on the direct health effects of the interventions and ignore the broader effects, partly because of a lack of solid evidence and controversial perspectives. Some studies highlighted concerns about the risks of overconsumption of zinc in public health interventions (Arsenault & Brown, 2003; Maret & Sandstead, 2006). With such a narrow gap between zinc recommended dietary allowance and the reference dose, there is little room for public health interventions to strike a balance between the benefits of alleviating zinc deficiency and the potential risks of zinc toxicity (Maret & Sandstead, 2006). Given that such interventions would affect the whole population, children and young adolescents who have a narrower window of intervention would be the most vulnerable groups to zinc deficiency and the hazards of excessive zinc intake. The safety of large-scale zinc supplementation also remains controversial. Some studies suggested that the intervention of zinc supplementation and food fortification should be scrutinized, especially among vulnerable groups, like, infants and toddlers. In the United States, for example, exposure to voluntary fortified foods and supplements was predicted to lead to excessive zinc intake in about 50% of children aged 1-3 years (Arsenault & Brown, 2003; Bailey et al., 2012; Butte et al., 2010; Sacco et al., 2013). Excessive zinc intake can lead to chronic zinc toxicity, which inhibits the absorption of copper and iron and ultimately induces persistent iron deficiency anemia (IDA) that is unresponsive to iron therapy (Agnew & Slesinger, 2021; Olivares et al., 2012). Therefore, indiscriminate supplementation with pharmacologically bioavailable zinc doses might not be ideal as a long-term intervention to combat zinc deficiency (Maret & Sandstead, 2006; Simpson et al., 2011). Nevertheless, clinical trials underpinned the safety of zinc supplementation, indicating that zinc supplementation projects pose little risk to public health (Fischer & Harvey, 2005). The controversies further confirm the need for research into the safety of zinc supplementation. Although there is no direct medical evidence to suggest that consuming fortified foods is safer than taking supplements, experts still tend to assume that the former poses fewer potential toxicity risks and is more benign (Hillebrandt & Engelbert, 2015). Although voluntary flour fortification is not as widespread in China as it is in other countries, such as the United States, it is still necessary to discuss the potential risks of excessive intake in advance to avoid future challenges.

Furthermore, consumers acceptance is vital for the promotion of health interventions, which is ignored in many of the current economic evaluation studies. Rabovskaja et al. (2013) initially considered consumer

perceptions as indirect cost when evaluating the economic effectiveness of mandatory fortification of folic acid in wheat flour in Australia, similar as De Steur et al. (2010a, 2010b, 2012) did for folate and multibiofortification in rice in China. This study will comprehensively evaluate and compare different zinc interventions. For the biofortification projects, zinc can be biofortified through conventional breeding, agronomic techniques, and biotechnologies. Some novel techniques, such as genetic modification, have successfully increased the zinc concentration in the endosperm, avoiding the antagonistic effect of phytic acid in the aleurone layer and elevating the zinc bioavailability in the human body (Cakmak, 2008). However, genetically modified (GM) foods remain controversial in Chinese society. There was a large amount of disagreement among the studies regarding the consumers' acceptance of GM biofortified foods. Some indicated that Chinese consumers have an average negative attitude (Hu et al., 2006; Jin, 2014; Zheng et al., 2018), while others reported that they are willing to pay premiums, especially for GM biofortified foods with enhanced micronutrients content (De Steur et al., 2010a, 2010b, 2015; Li et al., 2002).

Overall, past literature on zinc intervention evaluations did not comprehensively include the possible adverse outcomes and social impacts, nor conducted sensitivity analysis and relied on simplistic modeling in the evaluation. To the best of our knowledge, this study is the first to compare the cost-effectiveness of different public health interventions designed to alleviate zinc deficiency by using the Markov model, taking into account both the potential risks and how the general consumers perceive them.

The goals of this research are twofold: (1) to conduct a comprehensive evaluation of the cost-effectiveness of alternative zinc deficiency interventions and (2) to determine the most cost-effective intervention approach by comparing the economic outcomes of interventions derived under different scenarios.

2 | METHODOLOGY AND DATA COLLECTION

CEA is a decision-making assistance tool that facilitates the comparison of given programs to determine whether the effectiveness of an intervention justifies its cost, and is widely implemented in the field of public health, such as disease control (Mangen et al., 2007), nutritional improvement (De Steur et al., 2012; Stein et al., 2005), and risk management (Caswell & Jensen, 2007; Malcolm et al., 2004). To compare the cost-effectiveness of alternative interventions to alleviate zinc deficiency in China and eliminate the differences between studies, our study provided an ex ante analysis with real-world data from cohort studies and project reports. Additionally, we considered the potential risks of the interventions in our model and set up several scenarios based on the variation of reality to better understand the impacts.

We constructed a decision-analytic Markov model to evaluate the cost-effectiveness of three zinc deficiency interventions (i.e., zinc supplementation, food fortification, and biofortification) in China under different scenarios by using Microsoft Excel 2017. In our model, we accounted for both the direct costs and the indirect costs of implementing the project, including potential risks of excessive zinc intake and consumers' latent preference/ discount towards these interventions.

Markov models are the most frequently used model in health economic evaluation (Kuntz & Weinstein, 2001). Its ability to consider the problems with continuous risks enables a more accurate representation of the evaluated projects. Compared with traditional economic evaluation models, the Markov model can easily capture recurrent events and provide decision-making support under uncertainties (Barton et al., 2004; Kuntz & Weinstein, 2001). Studies have shown that Markov models are applicable and suitable for assessing the cost-effectiveness of public health interventions, such as micronutrient supplementation and food fortification (Dainelli et al., 2017; Rabovskaja et al., 2013). The wide-ranging adoption of the Markov model in studies demonstrates the flexibility of its framework, which renders room for researchers to construct a model based on real-life setting to facilitate decision-making in public health intervention.

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A Markov model yields a social perspective analysis as the individuals are diagnosed, treated, and released from medical care. Considering the costs involve both one-time and periodic payments (e.g., the initial cost of R&D for biofortification and continuous cost in later years for maintenance) we assumed a 30-year time horizon in which the cost and benefits are calculated and simulated during the duration of the implementation of the intervention, taking into account the natural history of pneumonia infection and persistent IDA using a sequence of transitions among health states. The setting of a 30-year time horizon is primarily grounded on two key considerations. First, as suggested by Haacker et al. (2020), the selected time horizon should last until the steady state is achieved to deliver valuable results in an economic evaluation. Most of the cost-effective analyses about fortification and supplementation projects selected duration ranged from 5 to 30 years (De Steur et al., 2012; Horton, 2006; Li & Zhang, 2016). In that sense, a 30-year time horizon can indeed more fully capture the cost and benefits of changes. Following Carter et al. (2009), we made the assumption that all interventions would operate in a "steady-state" manner. Figure 1 illustrates the decision tree for 1 year of zinc interventions. The subbranches for intervention, which represent whether the individual is under the intervention's coverage, are followed by the subbranches for three health states, including zinc deficiency (Figure 1A), excessive zinc intake (Figure 1B), and no disease. For the zinc intake situations, we assigned 27% of the target population to the "zinc deficiency" state, while 1% start from the "excessive intake" state, which is based on the previous meta-analysis conducted in China (Cai-Jin et al., 2021; Yan, 2021). In Figure 1A, patients with pneumonia would either die, recover, or get infected in the following round/year. Those who are cured would progress to zinc intake status, which is on the next branch of the decision tree, but they would still be susceptible to reinfection. The interventions (zinc supplementation, fortification, or biofortification) would decrease the probability of getting pneumonia in the zinc-deficient populations.

Different from past cost-effectiveness research, we also considered the impact of excessive zinc intake. In Figure 1B, for individuals exposed to excessive zinc intake and IDA simultaneously, persistent IDA is assumed to happen in 100% of the cases, which can be either treated or irreversible.



FIGURE 1 Decision tree structure. The initial node in the decision tree presents two options: the implementation of zinc intervention(s) or maintaining the current status. Following this decision, patients in each arm are introduced into a Markovian state-transition model, wherein they progress through various health states on an annual basis.

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The target population in our study was children in China aged 5–14. Different health states would generate various costs, and result in different health impacts. To compare the incremental cost-effectiveness ratio (ICER) of different interventions and facilitate decision-making, the "no intervention" scenario was set as the baseline.

Our analysis was based on second-hand data, including national census statistics, peer-reviewed studies, published reports, and expert opinion. As summarized in Table 1, the data included epidemiological information on the population, costs and efficacy of the interventions, and health outcomes derived from medical research. The epidemiological data were comprised of population size, the incidence of pneumonia in children and adolescents, the prevalence of IDA, and the death rate. the relative risk (RR) of pneumonia in the group exposed to various interventions, the probability of excessive zinc intake, and the cost of the interventions were also utilized in the assessment. Different scenarios were set up based on previous consumer research of biofortified crops developed with and without GM techniques. Adjustments were also made in scenarios to adapt future costs and benefits to their net present value. As for the outcomes, quality-adjusted life years (QALYs) gained across the population and ICERs were reported and compared to verify the cost-effectiveness of several interventions under different scenarios. We judged the cost-effectiveness according to WHO-CHOICE, in which an intervention is considered to be highly cost-effective when the cost per QALY is less than the country's annual gross domestic production (GDP) per capita (Marseille et al., 2014). The range of cost-effective interventions falls between one and three times GDP per capita. If the cost per QALY exceeds three times GDP per capita, then it is not considered costeffective. It is notable that in some cases, the savings from reduced medical costs may outweigh the intervention expenses, resulting in a negative net cost. Thereby, the CE plane, developed by Black (1990) to facilitate the interpretation of costeffectiveness criteria in medical decision-making, is used to graphically interpret our findings.

2.1 | The health efficacy of interventions

The relationship between the interventions and the risk of pneumonia is derived from related RCTs. Due to a lack of research on Chinese children, the efficacy of preventive zinc supplementation and food fortification was based on a systematic review of 18 cohort studies conducted by Bhutta et al. (2013), in which they found that pneumonia in developing countries would reduce by 19% (95% confidence interval [CI] 10-27, p = 0.05) at the post-intervention stage. The efficacy of zinc-biofortified wheat flour is based on the study of Sazawal et al. (2018), a community-based, doublemasked RCT with 2893 children. These participants received zinc-biofortified wheat flour with high zinc contents to consume for 6 months. The results showed that high zinc wheat flour could reduce the prevalence of pneumonia in children by 17% (95% Cl 6%-31%, p = 0.05). Considering that the evidence for zinc biofortification was derived from a single RCT, in which 10 ppm extra zinc was consumed from biofortified wheat by Indian children with low zinc plasma levels, it is necessary to adjust this evidence to extrapolate their findings to our target population. A common strategy for extrapolation is using the Bayesian method (Khosrowi, 2023). Previous studies proved that the effectiveness of consuming supplemental zinc could be a predictor of the population zinc status. For instance, the effectiveness of supplemental zinc is greater among populations with a higher prevalence of zinc deficiency (Hotz, 2001). There is also a linear relationship between the effect size of zinc intervention and the zinc status of the population (Gibson et al., 2008; Hess et al., 2007). Therefore, it is reasonable to assume a direct linear relationship between the prevalence of zinc deficiency and the effect size (RR ratio) of zinc interventions. This assumption is based on evidence that zinc interventions tend to have significant impacts on population with low zinc serum concentration levels while having a limited impact on population with normal zinc status (Gibson et al., 2008; Hess et al., 2007). As the prevalence of zinc deficiency in Chinese children was estimated to be around 27% (Cai-Jin et al., 2021) and 85.8% in Indian children in RCT (Sazawal et al., 2018), the RR of consuming biofortified wheat to pneumonia in Chinese children was adjusted to 0.95 (95% CI 0.91-0.98, p = 0.05) by using the Bayesian method with an adaptive Metropolis-Hastings (MH) algorithm. We illustrate the process of extrapolation in Supporting Information Appendix C. While this method can be helpful in providing analysis and support for decision-making, it is crucial to discuss the limitations of the results drawn from the assumptions underlying this approach (Wang et al., 2019), which we have specified in the discussion section.

	Value in the base	The range used in the one-	PSA		
Parameter	scenario	way sensitivity analysis	SE	Distribution	Source
Epidemiology					
Population scale of children aged 5-14, million	168.92	I	ı	I	The State Council (2021)
Prevalence of pneumonia, %	12.6	9.45, 15.75	0.02	β	Sun et al. (2020)
Prevalence of anemia, %	8.9	6.68, 11.13	0.01	β	China National Children's Center (2020)
Prevalence of zinc deficiency, %	27	20.25, 33.75	0.02	β	Cai-Jin et al. (2021)
Probability of zinc intake > UL, %	1	0.75, 1.25	0.002	β	Yan (2021)
RR risk of excessive intake (zinc supplementation)	1.45	1.09, 1.81	0.11	В	Wallace et al. (2014)
RR risk of excessive intake (zinc fortification)	1.42	1.07, 1.78	0.11	β	Sacco et al. (2013)
RR risk of excessive intake (biofortification)	1.42	1.07, 1.78	0.05	β	Assumed to be the same as the risk ratio of consuming fortified food
Probability of persistent iron deficiency anemia when zinc intake > UL for anemia patient	100%	I	I	I	Assumed by authors
Death rate	Various	Various	Various	I	The State Council (2021)
The coverage rate of the intervention	45%	30%, 60%	I	I	Assumed by authors
Efficacy					
Pneumonia RR risk (zinc supplement)	0.81	0.6, 0.9	0.05	В	Yakoob et al. (2011)
Pneumonia RR risk (food fortification)	0.81	0.6, 0.9	0.04	β	Yakoob et al. (2011)
Pneumonia RR risk (biofortification with breeding)	0.83	0.6, 0.9	0.02	β	Sazawal et al. (2018)
Pneumonia RR risk (biofortification with zinc fertilizer)	0.83	0.6, 0.9	0.02	В	Sazawal et al. (2018)
					(Continues)

TABLE 1 Summary of parameters in the Markov model.

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	Value in the base	The range used in the one-	PSA			
Parameter	scenario	way sensitivity analysis	SE	Distribution	Source	
Health outcomes						
QALY weights	0.985	0.93, 1	0.02	β	EQ-5D-3L study conducted by Yao et al. (2019)	
Disability weight for pneumonia	0.21	0.16, 0.26	0.04	β	Salomon et al. (2012)	
Disability weight for anemia	0.058	0.044, 0.073	0.02	β	Salomon et al. (2012)	
Costs						
Zinc supplementation (per capita), USD	6.61	4.96, 8.26	6.61	٨	Derived from Horton (2006)	
Food fortification (per capita), USD	0.298	0.22, 0.37	0.298	٨	Derived from Horton (2006)	
Biofortification with breeding, USD	0.01	0.008, 0.013	0.01	٨	Derived from Li and Zhang (2016)	
Biofortification with zinc fertilizer, USD	0.2	0.15, 0.25	0.2	*	Derived from zinc fertilizer usage data by Wang et al. (2003) and online zinc fertilizer prices as listed below	
Zinc fertilizer (ZnSO ₄ ·7H ₂ O) usage per hectare, kg	30	1	I	I	Wang et al. (2003)	
Zinc fertilizer (ZnSO4·7H2O) price per kg, USD	0.6	I	I	I	Authors estimate based on the online price information	
Wheat production volume, kg per hectare	5912.3	I	I	I	China National Bureau of Statistics (2021)	
Wheat plantation area in 2021, hectare	22,962,000	1	I	I	China National Bureau of Statistics (2021)	
Pneumonia treatment cost, USD	91.89	68.9, 114.9	91.89	٨	Modeled based on the components listed below	
Cost pneumonia hospitalized, USD	1183.97	I	I	I	National Health Commission (2021)	
Pneumonia hospitalization rate, %	1.33	I	I	I	Lu et al. (2019)	
Cost pneumonia nonhospitalized, USD	77.5	I	I	I	Medical practitioners' estimates	
Anemia treatment cost, USD	50.2	37.7, 62.8	50.2	٨	Derived from online price information	

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	Value in the base	The range used in the one-	PSA		
Parameter	scenario	way sensitivity analysis	SE	Distribution	Source
Annual wheat consumption per person, kg	66.4	1	I	I	Derived from China National Grain & Oils Information Center (2022)
Annual wheat consumption volume, million tonnes	93.8	1	I	I	China National Grain & Oils Information Center (2022)
Wheat price, USD/kg	0.49	1	I	I	National Bureau of Statistics (2022)
WTP discount for GM biofortified crops	-20%	-10%, -40%	I	I	Authors' assumptions based on previous research
WTP premium for GM biofortified crops	20%	10%, 40%	I	I	Authors' assumptions based on previous research
WTP premium for non-GM biofortification	36.5%	1	I	I	De Steur et al. (2014)
WTP premium for zinc supplementation	19%	I	I	I	De Steur et al. (2014)
WTP premium for zinc fortification	19%	I	I	I	Assumed by authors
			-		

Note: The direct cost includes the cost of intervention and the opportunity costs of formal healthcare goods and services, covering the cost of intervention implementation, medical nonhospitalized × (1 - pneumonia hospitalization rate); Anemia treatment cost = cost anemia hospitalized × anemia hospitalization rate + cost of anemia nonhospitalized × (1 - anemia expenses for pneumonia treatment, and anemia treatment. Pneumonia treatment cost = cost pneumonia hospitalization rate + cost pneumonia hospitalization rate); Intervention cost = cost of zinc intervention per capita × population of target group;

Indirect cost refers to the cost of consumers utility or welfare, which is monetarized by WTP. Indirect cost = utility cost of consumers derived from the intervention x annual wheat Abbreviations: GM, genetically modified; PSA, probabilistic sensitivity analysis; QALY, Quality-adjusted life year; RR, relative risk; UL, upper intake level; WTP, willingness-to-pay. consumption volume = (WTP premium or discount for interventions × wheat price) (annual wheat consumption per person × population of target group).

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2.2 | Epidemiology data

The prevalence of pneumonia among children aged 5–14 in China was estimated to be 12.6% (Sun et al., 2020). When zinc interventions were implemented, the probability of persistent IDA under different interventions was calculated based on the prevalence of IDA and the likelihood of excessive zinc intake. Following the aforementioned rationale, we assumed a linear relationship between the prevalence of excessive zinc intake and RR value to extrapolate the data from other countries to our target population using the Bayesian method with an adaptive MH algorithm. The RR of excessive zinc intake in groups consuming supplements or (bio)fortified foods is estimated to be 1.15 (95% CI 1.12–1.19, p = 0.05) and 1.14 (95% CI 1.11–1.18, p = 0.05), respectively, adjusted from studies undertaken in the United States as presented in Table 1 (Arsenault & Brown, 2003; Sacco et al., 2013; Wallace et al., 2014). The process of extrapolation is illustrated in detail in Supporting Information Appendix C. On the basis of the zinc intake distribution among Chinese children (Yan, 2021), the risk of surpassing the upper limit is expected to be relatively low (1% on average). From a conservative point of view, it is assumed that with the compliance of the intervention, 100% of the children who suffer from IDA and zinc overdose simultaneously would have persistent IDA.¹

Given the absence of evidence on the risk of overconsumption of interventions' in the context of China, we used the data extracted from Sacco et al. (2013) and, as previously noted, assumed a linear relationship for target population adjustment in our model. Given that Western customers' dietary patterns are expected to differ from those of Chinese consumers, one must carefully interpret the findings. Therefore, we thoroughly considered the data uncertainties and applied variation ranges in our sensitivity analysis.

The interventions' coverage rate was assumed to be 45% in the baseline model with a range from 30% to 60% in the sensitivity analysis to combat the uncertainty. This assumption was based on the previous studies conducted by De Steur et al. (2012) and Li and Zhang (2016), in which they estimated the biofortification coverage was 30% for the pessimistic scenario and 60% for the optimistic scenario.

2.3 | Health outcomes

QALYs gained per year of zinc supplementation, food fortification, and biofortification were used to measure the benefits of the interventions. The QALYs utility weights of healthy individuals were adjusted by the average health status weights derived from the EQ-5D-3L scores of the Chinese population, which is 0.985 for normal healthy people (Yao et al., 2019). According to the disability weights measurement study by Salomon et al. (2012), the disability weight for children with pneumonia and anemia is estimated to be 0.21 and 0.058, respectively.

2.4 | Costs of diseases and interventions

In our estimation, we considered not only the direct cost of implementation and medical cost savings of pneumonia incurred by the interventions, but also the indirect cost derived from excessive zinc intake. According to the China Health Statistical Yearbook 2021, the average medical expense of hospitalization of pneumonia in public hospitals is 7638 CNY (1183.97 USD) per case (National Health Commission, 2021). It is noteworthy that this cost only covers the expenditure in public hospitals not in other medical systems. According to Li et al. (2017) and Lu et al. (2019), the hospitalization rate of pneumonia among children in China is around 1.3%. Therefore, assuming that the drug cost for common respiratory infection is 500 CNY (77.5 USD), which is based on the practitioners' assumption, we estimated the pneumonia cost to be 592.79 CNY (91.89 USD) per capita.

The average cost of the IDA is calculated according to the price and related information of a common drug for treating anemia, derived from online drug information (http://www.china-yao.com/), in which the national average cost of iron polysaccharide complex capsules is 3.5 CNY (0.54 USD) per capsule. Since the dose for children is one capsule per day for 3 months, we estimated that the annual cost of persistent IDA caused by excessive zinc intake is 323.9 CNY (50.2 USD) per capita. Due to a lack of comparable data, these expenses also do not reflect the expenditures to the whole healthcare system.

The cost of biofortification through breeding techniques is evaluated based on the studies conducted by De Steur et al. (2012), Li and Zhang (2016), and Liao (2020). The costs consist of initial research and development costs and the ongoing costs of variety extension, maintenance, and government regulation. The commercialization of biofortified crops in China mainly goes through three stages, namely, cultivation, extension, and maintenance. In the cultivation stage, capital investment is needed to support the research and development of biofortified crops. It is reported that the cost of cultivating a new biofortified variety in China would be approximately 1,760,000 CNY (272,817.5 USD). The extension cost is reported to be around 45–60 CNY (6.98–9.3 USD) per acre per year. And the extension duration would be approximately 4–6 years. Therefore, with a 45% coverage rate and a domestic wheat plantation area of 22.91 million acres in 2021, the average total cost of extension would be close to 465 million CNY (72.1 million USD). The maintenance duration for crops is about 20 years, with an annual maintenance cost of 5%–10% of the cultivation cost. Therefore, the average yearly cost of biofortification with breeding techniques would be around 0.01 USD/capita. This estimation is consistent with the study conducted by Ma et al. (2008).

The cost of biofortification through an agronomic approach is evaluated based on the fertilizer usage data from Wang et al. (2003) and web-based price information (0.54 USD/kg for zinc sulfate heptahydrate as the most commonly applied zinc fertilizer). Given that an average of about 30 kg/acre is required to effectively increase soil available zinc to a high zinc level, the cost per acre would be approximately 16.28 USD. On the basis of the domestic wheat production and consumption data, the per capita cost of biofortification through zinc fertilizer is estimated at 0.27 USD. The costs of zinc supplementation and zinc food fortification are derived from the estimates of Horton (2006) and Ma et al. (2008).

All costs were adjusted to be representative of the Chinese price level in 2021. We adjusted for price differences between different regions using health sector price indices reported by the World Bank's International Comparison Program for cost inputs collected from other settings. To adjust for inflation, we converted the costs into Chinese yuan using the exchange rate for the year reported by the Bank of China at the first step, and then inflated prices to 2021 levels using the World Bank GDP deflator.

2.5 | Consumers' choice and perception

Among the various methods of micronutrient enrichment, GM breeding techniques are still a very controversial technology and most likely to raise public concerns over the human and environmental safety (Adenle et al., 2013; González et al., 2009), which may have more ambiguous effects on the costs of societal welfare. Therefore, to better account for these societal implications, our study monetized consumers' perceptions to provide a more comprehensive analysis of the cost-effectiveness of different interventions. Following Rabovskaja et al. (2013), we referred consumers positive and negative willingness-to-pay (WTP) as premium and discount, respectively. Table 1 lists the WTP premium and discounts for each of the interventions with references. Due to the research gap on consumers WTP on food fortification, we assume that fortified products share the same WTP premium with supplementation. For the biofortification with transgenic breeding techniques, several studies indicated that Chinese consumers have an average negative attitude towards GM biofortified foods (Jin, 2014; Zheng et al., 2018). Discounts for GM technologies offered by Chinese consumers ranged from 14% to 37% (Hu et al., 2006; Jin, 2014; Zheng et al., 2018). However, studies diverged significantly on this issue. It had also been reported that Chinese consumers hold positive attitudes towards GM biofortified foods (De Steur, et al., 2013, 2015; Li et al., 2002). The premium fell between 19% and 34%.

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Taking into account the heterogeneity of Chinese consumers acceptance of GM biofortified crops, where different target micronutrients or populations may account for differences between studies, we considered both the case in which GM food is preferred (premium) or not (discount) in our sensitivity analysis. The average annual consumption of wheat grain is 66.4 kg/person. Assuming that the average price is 3.15 CNY (0.49 USD)/kg, which is based on the average price extracted from the National Bureau of Statistics (2022), the average annual cost from consumer discounts would range from 16.5 to 65.9 CNY (2.6–10.2 USD) per person. At the same time, the average welfare gain from consumers' surplus was assigned the same range. Following the same rationale, as presented in Table 1, we employed various consumers WTP premium/discount for non-GM biofortification, supplementation, and food fortification, with values of 36.5% premium, 19% premium, and 19% premium, respectively (De Steur et al., 2014). Due to the research gap on consumers WTP on food fortification, we assume that fortified products share the same WTP premium with supplementation. Given the uncertainty of the assumptions about consumers' perceptions, we opted to evaluate their impact in the sensitivity analysis rather than in the baseline scenario.

2.6 | Timing

The time horizon used in this study is 10 years, as micronutrient interventions can have a long-term impact on population health. Following the guidelines of National Institute for Health and Care Excellence (2014), we set the discount rate at 3.5% to convert future costs and benefits into present values. The discount rates used in the sensitivity analysis are 0% and 5%.

2.7 | Uncertainty

The baseline results were based on the best available estimates from the literature (Table 2). To accommodate for uncertainties, we conducted a sensitivity analysis and implemented variations for several parameters in our model.

We conducted a one-way deterministic sensitivity analysis to evaluate the impact of each of the parameters on cost-effectiveness. We applied ±25% variations to all costs, risk ratios, diseases prevalence, utility weight of the diseases, and appropriate variations to QALY of the average healthy individuals. All variations in one-way sensitivity analysis were provided in Table 1. Furthermore, several scenarios were set to include the impact of both consumers' perception and discount rate.

	Cost	ΔCost	QALY	ΔQALY	ICER
Supplementation	138.75	49.52	8.3	0.04	1312.13
No intervention	89.23	-	8.26	-	-
Fortification	75.76	-13.48	8.3	0.04	-355.51
No intervention	89.23	-	8.26	-	-
Biofortification with breeding technique	85.53	-3.76	8.27	0.01	-410.24
No intervention	89.23	-	8.26	-	-
Biofortification with the agronomic approach	87.42	-1.18	8.27	0.01	-200.87
No intervention	89.23	-	8.26	-	-

TABLE 2 Cost-effectiveness of different zinc interventions in the base scenario.^a

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

^aNumbers are on a per person of interventions basis. The currency of cost is USD.

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Furthermore, a microsimulation model was conducted to capture the stochastic nature of events among individuals within the cohort to tackle the first-order uncertainty. Our Markov microsimulation model was run for 1000 cohorts. Second-order uncertainty was also considered in our study. We use probabilistic analysis to vary the parameters concurrently. The following parameters are adjusted with a range with variation (1) probability of pneumonia infection, (2) possibility of persistent IDA under different interventions, (3) costs of diseases, (4) costs of different intervention strategies, (5) efficacy of the interventions, (6) costs induced from consumers perception, and (7) health outcomes (see Table 2).

Following Tengs and Wallace (2000), we inferred the distribution of all costs by assuming a γ -distribution, while we inferred probabilities and utilities by assuming a β -distribution and estimated the standard error (SE) that minimizes the sum of squared error to predict the population's zinc intake distribution and the related health impacts.

3 | RESULTS AND DISCUSSION

This section presents the results and implications of our decision-analytic model, including the CEA of the interventions, the deterministic sensitivity analysis (i.e., one-way sensitivity analysis and scenario analysis), and the probabilistic sensitivity analysis.

3.1 | Cost-effectiveness of the interventions

We compared the ICERs of the four interventions, that is, zinc supplementation, food fortification, biofortification with breeding techniques, and biofortification with an agronomic approach (no intervention as the baseline). The results are presented in Table 2. We judged the cost-effectiveness of the interventions based on the WTP threshold, which is the policymakers' maximum willingness to pay for a unit of health outcome.

Compared with the benchmark (no intervention), zinc supplementation, fortification, and biofortification would all be highly cost-effective interventions that could provide QALY gains at an acceptable cost, or even at a reduced cost. In the 10-year model, compared with supplementation or food fortification, biofortification, especially when developed through breeding, is considered the most cost-effective method to alleviate zinc deficiency among the Chinese population, resulting in the largest QALY at the lowest cost. If biofortification is implemented using breeding techniques and 45% compliance is achieved, the intervention would save 14.22 USD and gain 0.03 QALY per person per year. The ICER of the interventions shows that in the base scenario, all four interventions can be regarded as cost-effective since the ICER is lower than the threshold of 11,943 USD. Compared with other zinc interventions, biofortification using breeding techniques could cost 1722 USD less per QALY gained than supplementation, and induce 55 USD more in cost savings per QALY gained than food fortification. Despite the methodological differences with previous economic evaluation studies, our results are generally consistent with the zinc studies by Liu et al. (2017) and Ma et al. (2008), indicating that the benefits of long-term, large-scale zinc food fortification, and biofortification outweigh the losses for the Chinese population.

Our study highlights the importance of considering the risks of overconsumption when evaluating micronutrient interventions. Although zinc supplementation is still a highly cost-effective approach in our estimation, more scientific evidence is needed to assess the potential adverse impacts of zinc overdose in the whole population. As such, large-scale indiscriminate distribution of zinc supplementation might not be an effective way to combat zinc deficiency in children in developed regions where the risks associated with excessive intake may outweigh the loss deprived from zinc deficiency. This conclusion is consistent with Maret and Sandstead (2006), who suggested that long-term zinc supplementation should not be conducted as a public policy intervention without careful supervision. Also indiscriminate addition of food fortificants is a matter that deserves further attention since foods are increasingly being fortified with micronutrients (Allen et al., 2006; Jia et al., 2016). The situation of excessive zinc intake in the population induced by fortified foods has already been reported in some of

the high-income regions/countries, such as the United States, where the addition of food fortificants increased the percentage of children exceeding the zinc intake UL to 18%-24% (Fulgoni, 2011). A similar conclusion had been reached by studies on European children as well (Flynn et al., 2009). Given the limited number of clinical trials that have assessed the impact of excessive zinc from fortified foods on iron absorption in the human body, we assumed that the incidence of persistent IDA is 100% for individuals exposed to excessive zinc intake and IDA simultaneously. Besides, we also did not consider the potential opportunity cost derived from the work leaves of the sick children's parents due to the lack of data. Therefore, these overlooked factors would result in an underestimation of the costs. More dose-response and toxicity data are also expected in the future to assess the adverse impact of excessive zinc intake for a better evaluation of cost-effectiveness.

3.2 | Deterministic sensitivity analysis

We conducted one-way and probabilistic sensitivity analysis to evaluate the robustness of the baseline results. As shown from the tornado diagram in Figure 2, we applied a ±25% variation to all costs and appropriate ranges for other parameters as listed in Table 2. The one-way sensitivity analysis showed that the RRs extracted from interventions' efficacy studies have the highest impacts on the final cost-effectiveness, followed by the utility weights of pneumonia. In contrast, the coverage rate of the intervention, death rate of pneumonia and anemia, and QALY weights had the lowest impacts.

Table 3 provides the findings of the sensitivity analysis under different scenarios. With the inclusion of customers' perceptions, the ICER result varied considerably, which is consistent with previous research (Rabovskaja et al., 2013). This suggests that consumers perceptions can significantly affect economic evaluation outcomes. Assuming the WTP for one QALY gained is 80,976 CNY (11,943 USD), that is, the per capita GDP of China in 2021, biofortification based on transgenic breeding techniques is still cost-effective when consumers' willingness to pay



FIGURE 2 Tornado diagram of one-way sensitivity analysis. The outcomes of a one-way sensitivity analysis, aiming to identify influential model variables, were presented in a tornado diagram. This diagram depicts the factors in descending order of their variation in value, showcasing their respective impacts on the final ICER results. ICER, incremental cost-effectiveness ratio.

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	ICER (ΔCost/ΔQA	ιLY ^a)			
Scenario	Supplementation	Fortification	Biobreeding (GM)	Biobreeding (non-GM)	Bioagronomy
Base scenario	1312.13	-355.51	-410.24	-410.24	-200.87
Discount rate, 0%	1041.64	-367.47	-411.87	-411.87	-234.67
Discount rate, 7%	1605.07	-342.53	-408.44	-408.44	-164.20
Consumers WTP (optimistic acceptance to GM, +40%)	-325.86	-1986.44	-14,822.73	-13,560.81	-13,351.4
Consumers WTP (pessimistic acceptance to GM, -40%)	-325.86	-1986.44	13,990.69	-13,560.81	-13,351.4

TABLE 3Results of the scenario analysis.

Abbreviations: GM, genetically modified; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; WTP, willingness-to-pay.

^aThe currency of cost is USD.

for GM food is lower than 34% than the conventional alternative. However, if consumers discount GM wheat flour by 40%, which is the lowest level of the consumer discount for GM crops estimated by Zheng et al. (2018), the ICER would exceed the threshold and not be cost-effective. The ICER results of other interventions (non-GM biofortification, fortification, and supplementation) still indicate cost-effectiveness, as consumers generally hold a positive attitude towards these techniques. We suggested that the intangible costs of the program, such as societal impacts, should be considered in health intervention projects.

For policymakers to maximize the benefits of these novel techniques, they should take into account public opinions, which drive compliance, through timely communication of the scientific information to the consumers. As shown earlier, consumer perceptions can change cost-effectiveness results to a great extent. Additionally, if a large share of consumers does not positively evaluate transgenic techniques, it will be hard to achieve large-scale coverage.

3.3 | Probabilistic sensitivity analysis

In this analysis, a Monte Carlo simulation was conducted to estimate the SE of each parameter, by which interventions' efficacy is assumed to follow the beta distribution while costs comply with the gamma distribution. The ICER results generated from the simulated scenarios are located right below the line through the origin, which is the WTP threshold (11,943 USD). This shows that all zinc interventions were cost-effective in most of the simulation rounds. In our 1000 times simulation, the percentage with cost-effective results that fell short of the ICER threshold is 100% for biofortification (breeding techniques), 99.8% for biofortification (agronomic approach), 94.1% for zinc supplementation, and 99.9% for food fortification. Zinc-biofortified wheat flour with breeding techniques was again preferred over zinc supplementation, food fortification, and biofortification with an agronomic approach. These results generally confirm the robustness of the baseline results.

However, the results need to be interpreted with caution, as China is a country with unbalanced socioeconomic development and diversified regional dietary habits. In our estimation, we extrapolate findings from meta-studies as well as RCTs conducted in other countries. Although adaptions have been made to fit the data to our target population, a regional assessment with local data would be necessary to further validate our findings. Lack of the whole-life analysis is another limitation of our estimations. The interventions are expected to impact humans throughout their entire lives. However, our estimation only took into account the impact on children and the adolescents' period. As most of the accessible medical evidence focuses on



FIGURE 3 Results of Monte Carlo Simulation (Probabilistic Sensitivity Analysis). Scatterplots were employed to superimpose the cost-effectiveness plane, demonstrating scenarios where implementing zinc interventions proved more or less cost-effective compared with having no intervention. These scatterplots were generated from the outcomes of Bayesian multivariate probabilistic sensitivity analyses. To aid interpretation, a dashed line intersecting the cost-effectiveness plane represented the willingness-to-pay threshold. QALYs, quality-adjusted life-years. QALYs, quality-adjusted life years.

children and adolescents, the life cycle assessment is impractical due to lack of data on zinc intake status and intervention effectiveness of all age groups and genders. Besides, we had not distinguished the cost difference between GM and conventional breeding, which is also a limitation of this study. Further research is required to address the specific costs relating to different biofortification techniques to make comparisons in a more accurate way (Figure 3).

4 | CONCLUSION

This study shows that zinc biofortification and food fortification, and to a lesser extent, large-scale zinc supplementation, are highly cost-effective in alleviating the disease burden of zinc deficiency in China. Importantly, consumer perceptions towards these health interventions might significantly alter the outcomes. While this research is likely to advance China's nutrition programs by providing empirical evidence for decision-making in zinc deficiency reduction, there are some drawbacks to our current research approach. Due to a reliance on international data in the event that China-specific data was lacking, our results might not entirely reflect the potential impact of interventions and, hence, the real-life cost-effectiveness. To account for such uncertainties, our study incorporated a sensitivity analysis to account for this. Furthermore, we assumed that the probability of persistent IDA was applied to 100% of the individuals who both suffer from excessive zinc intake and IDA. This assumption would overestimate the indirect cost of zinc supplementation since the excessive risks induced by zinc supplementation were estimated to be higher than those associated with other interventions. In addition, we have not considered regional differences in the evaluation, which would further improve the variations in the applicability of the interventions at the local level. As the findings of our robust model underline the value of each of the examined strategies in terms of cost-effectiveness,

region-specific targeting and deployment of these complementary interventions may also provide a potential avenue for tackling the problem of zinc deficiency in a sustainable way. However, to ensure a successful deployment, future research is needed to develop and evaluate science-based marketing strategies for the implementation and promotion of zinc interventions and, if needed, for reducing potential intangible costs induced by consumers' negative perceptions.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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